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Interr al Application No
PCT/IB 00/01430

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 636 626 A (LABORATOIRES GLAXO SA) 1 February 1995 (1995-02-01) cited in the application claims 1-13	1-25
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Y	US 5 294 612 A (E. R. BACON ET AL.) 15 March 1994 (1994-03-15) claims 1-15	1-25
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Interr ... il Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/505 A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	H. W. HAMILTON ET AL.: "Synthesis and Structure-Activity Relationships of Pyrazolo'4,3-d!pyrimidin-7-ones as Adenosine Receptor Antagonists" J. MED. CHEM., vol. 30, no. 1, 1987, pages 91-96, XP002153808 tables I,,II ---	1-25
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2000	12/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

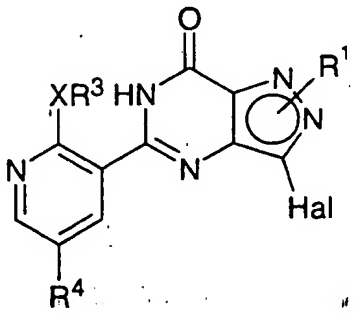
23. A compound of formula IIA, or of formula IIB, as defined in Claim 22.

24. Use as claimed in Claim 19, or method as claimed in Claim 20, wherein the condition is male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic dysfunction (FSOD).

25. Use as claimed in Claim 19, or method as claimed in Claim 20, wherein the condition is male erectile dysfunction (MED).

required) by hydrolysis and/or (if required) exchange with a further optionally substituted alkyl group;

(i) for compounds of formula I, in which R^2 represents optionally substituted lower alkyl (which alkyl group is branched and unsaturated at the carbon atom that is attached to the rest of the molecule), $NR^{12}R^{13}$, cyano, aryl or Het (which Het group is either aromatic or unsaturated at the carbon atom that is attached to the rest of the molecule), by cross-coupling of corresponding compounds of formula XXIV:



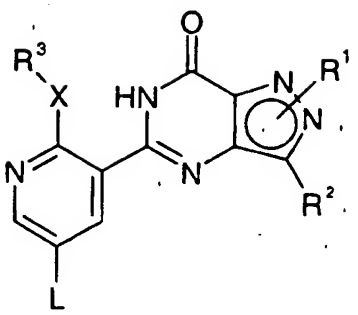
XXIV

wherein Hal represents Cl, Br or I, and R^1, R^3, R^4 and X are as defined in Claim 1, using a compound of formula

$R^{2a}M$

wherein R^{2a} represents optionally substituted lower alkyl (which alkyl group is branched and unsaturated at the carbon atom that is attached to M), $NR^{12}R^{13}$, cyano, aryl or Het (which Het group is either aromatic or unsaturated at the carbon atom that is attached to M), R^{12} and R^{13} are as defined in Claim 1 and M represents an optionally substituted metal or boron group, which group is suitable for cross-coupling reactions; or

(j) for compounds of formulae IA and IB in which R^2 represents lower acyl, lower alkoxycarbonyl or lower alkynyl, by a cross-coupling reaction between corresponding compounds of formula XXIV, respectively, as defined above, and a reagent or reagents capable of delivering the lower acyl, lower alkoxycarbonyl or lower alkynyl group (or groups equivalent to these).



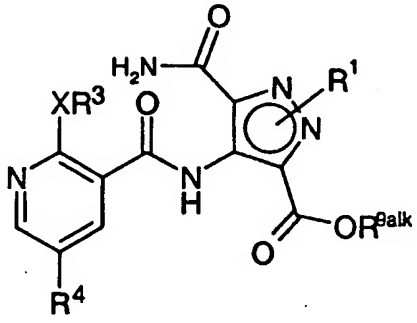
VIII

wherein L is a leaving group and R^1, R^2, R^3 and X are as previously defined for compounds of formula I, with a compound containing a group R^{4a} which is capable of exchanging for L;

(f) deprotection of a protected derivative of a compound of formula I;

(g) for compounds of formula I, in which R^2 represents $C(O)NR^{10}R^{11}$, and R^{10} and R^{11} are as defined previously for compounds of formula I, reaction of corresponding compounds of formula I, in which R^2 represents C(O)OH (or a carboxylic acid derivative thereof) with a compound of formula $HNR^{10}R^{11}$, in which R^{10} and R^{11} are as previously defined for compounds of formula I;

(h) for compounds of formula I, in which R^2 represents $C(O)OR^9$, cyclisation of corresponding compounds of formula VI:



VI

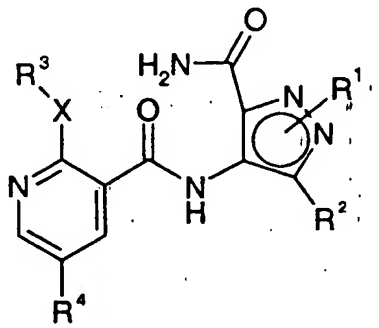
wherein R^1, R^3, R^4 and X are as defined previously for compounds of formula I, and R^{9alk} represents an optionally substituted lower alkyl group, as defined hereinbefore, followed by removal of the alkyl group R^{9alk} (if

therapeutically effective amount of a compound as claimed in any one of Claims 1 to 13 without the provisos to a patient in need of such treatment.

21. Use as claimed in Claim 19, or method as claimed in Claim 20, wherein the condition is male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic dysfunction (FSOD)

22. A process for the preparation of a compound of formula I, as defined in Claim 1, which comprises:

(a) cyclisation of a corresponding compound of formula II:



II

wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1;

(b) for compounds of formula I in which R^1 represents lower alkyl, Het, aryl, Het, aryl, alkylHet or alkylaryl (which latter five groups are all optionally substituted as defined hereinbefore in respect of R^1), alkylation of a corresponding compound of formula I, in which R^1 represents H;

(c) conversion, removal or introduction of a substituent on an aryl, or a Het, group in, or on the phenyl/pyridinyl, or pyrazolo, unit of, a compound of formula I;

(d) conversion of one R^3 group to another by alkoxide exchange or amino exchange for alkoxide;

(e) reaction of corresponding compounds of formulae VIII:

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]alanine;
5-{2-[2-(Dimethylamino)ethyl]-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl}-6-ethoxynicotinic acid; or
5-{2-[2-(Dimethylamino)ethyl]-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl}-6-ethoxy-*N*-methoxy-*N*-methylnicotinamide.

14. Compound as defined in any one of Claims 1 to 13 without the provisos for use as a pharmaceutical.

15. Compound as defined in any one of Claims 1 to 13 without the provisos for use as an animal medicament.

16. A formulation comprising a compound as defined in any one of Claims 1 to 13 without the provisos in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.

17. A formulation as claimed in Claim 16, which is a pharmaceutical formulation.

18. A formulation as claimed in Claim 16, which is a veterinary formulation.

19. The use of a compound as defined in any one of Claims 1 to 13 without the provisos in the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which inhibition of cGMP PDE5 is desired.

20. A method of treating or preventing a medical condition for which inhibition of cGMP PDE5 is desired, which comprises administering a

5-(5-Glycoloyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-[2-(4-morpholinyl)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-Acetyl-2-butoxy-3-pyridiyl)-2-[2-(4-piperidinyl)ethyl]-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one;

tert-Butyl 4-[2-(5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)ethyl]-1-piperidinecarboxylate;

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

[5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetic acid;

5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxynicotinonitrile;

1-Methyl-5-[2-propoxy-5-(1*H*-tetrazol-5-yl)-3-pyridinyl]-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-[5-(3-Hydroxy-5-isoxazolyl)-2-propoxy-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-Amino-2-propoxy-3-pyridinyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

{[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}acetic acid;

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]methanesulfonamide;

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]-3-oxo-β-alanine;

({[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}sulfonyl)acetic acid;

5-(2-Butoxy-5-iodo-3-pyridinyl)-2-[2-(4-morpholinyl)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

tert-Butyl 4-[5-(2-butoxy-5-iodo-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro -2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-piperidinecarboxylate;

tert-Butyl 3-[5-(2-butoxy-5-iodo-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro -2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-azetidinecarboxylate;

5-(2-Propoxy-5-iodo-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl]nicotinate;

tert-Butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetate;

tert-Butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]acetate;

[3-Ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetic acid;

[3-Ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]acetic acid;

5-(2-Propoxy-5-iodo-3-pyridinyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

2-[2-(Dimethylamino)ethyl]-5-(2-ethoxy-5-iodo-3-pyridinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

6-Butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]-*N*-methoxy-*N*-methylnicotinamide;

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-[5-Acetyl-2-(2-methoxy-1-methylethoxy)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

6-Isobutoxy-*N*,*N*-dimethyl-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)nicotinamide;

7. Compound as claimed in any one of Claims 1 to 6, wherein R^3 represents lower alkyl.

8. Compound as claimed in any one of Claims 1 to 7, wherein X is O.

9. Compound as claimed in any one of Claims 1 to 8, wherein R^4 represents halo, optionally substituted Het, optionally substituted aryl, $C(O)R^8$, C(O)AZ, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ or $NR^{16}Y(O)R^{17}$.

10. Compound as claimed in Claim 9, wherein R^4 is $COCH_3$ or NHB, wherein B represents H, SO_2CH_3 or C(O)Het.

11. Compound as claimed in any one of Claims 1 to 8, wherein R^4 represents iodo, lower alkyl, lower alkynyl (which latter two groups are substituted and/or terminated by $C(O)OR^9$ (wherein R^9 represents H or C_{1-6} alkyl)), $N(H)Y(O)R^{17}$, $N[Y(O)R^{17}]_2$, optionally substituted Het or $NR^{12}R^{13}$ (wherein R^{12} and R^{13} together represent C_{3-5} alkylene interrupted by O or $N\text{-}S(O)_2$-(optionally substituted aryl)).

12. Compound as claimed in Claim 11, wherein R^4 represents $N(H)Y(O)R^{17}$ (wherein R^{17} represents C_{1-4} alkyl optionally substituted and/or terminated by C(O)OH or C(O)O-lower alkyl) or lower alkynyl terminated by $C(O)O\text{-}C_{1-4}$ alkyl.

13. Compound as claimed in Claim 1, which is:
5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;
5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;
5-(5-Iodo-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

(ii) that R^4 is not NH_2 or NO_2 when: X is O; and R^2 is H, halo, optionally substituted lower alkyl, OR^6, $C(O)NR^{10}R^{11}$, $C(O)OR^9$, $NR^{12}R^{13}$, NHC(O)-lower alkyl, cyano, aryl, alkylaryl, Het or alkylHet (which latter four groups are optionally substituted); and

(iii) that R^4 is not H when: X is O; and R^2 is H, optionally substituted lower alkyl, OR^6, $C(O)NR^{10}R^{11}$, $C(O)OR^9$, $NR^{12}R^{13}$, NHC(O) - lower alkyl, cyano, aryl, alkylaryl, Het or alkylHet (which latter four groups are optionally substituted).

2. Compound as claimed in Claim 1, wherein R^1 represents optionally substituted lower alkyl.

3. Compound as claimed in Claim 2, wherein R^1 is lower alkyl, lower alkoxy-terminated lower alkyl, $NR^{12}R^{13}$-terminated lower alkyl, or *N*-morpholino-terminated lower alkyl.

4. Compound as claimed in Claim 1,wherein R^1 represents a 4-piperidinyl group, optionally substituted at the nitrogen atom of the piperidinyl group with lower alkyl or $C(O)OR^9$.

5. Compound as claimed in any one of Claims 1 to 4, wherein R^2 represents $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, lower alkyl optionally interrupted by one or more of O, S or N, optionally substituted at N by lower alkyl or acyl, or optionally substituted aryl or Het.

6. Compound as claimed in Claim 5, wherein R^2 represents $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, C_{1-4} alkyl optionally interrupted by O or N, optionally substituted at N by lower alkyl, optionally substituted phenyl, or optionally substituted pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrazin-2-yl, pyrazol-4-yl, oxadiazol-2-yl, furan-2-yl, furan-3-yl, tetrahydrofuran-2-yl and imidazo[1,2-a]pyridin-6-yl.

substituted by one or more lower alkyl groups and/or optionally interrupted by O or NR^{26})

R^{14} and R^{15} independently represent H or lower alkyl or R^{14} and R^{15}, together with the nitrogen atom to which they are bound, form a heterocyclic ring

R^{16} and R^{17} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$) or one of R^{16} and R^{17} may be Het or aryl, which latter two groups are both optionally substituted with lower alkyl

R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24} and R^{25} independently represent H or lower alkyl

R^{18} and R^{19} independently represent lower alkyl

R^{21} represents lower alkyl or aryl

R^{26} represents H, lower alkyl, aryl, $C(O)R^{27}$ or $S(O)_2R^{28}$

R^{27} represents H, lower alkyl or aryl

R^{28} represents lower alkyl or aryl

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen and/or sulfur

with the provisos:

(i) that R^4 is not NH_2 when: R^1 is C_{1-3} alkyl optionally substituted with phenyl, Het or a N-linked heterocyclic group selected from piperidinyl and morpholinyl; wherein said phenyl group is optionally substituted by one or more substituents selected from C_{1-4} alkoxy; halo; CN; CF_3, OCF_3 or C_{1-4} alkyl wherein said C_{1-4} alkyl group is optionally substituted by C_{1-4} haloalkyl or C_{1-4} haloalkoxy either of which is substituted by one or more halo atoms; and R^2 is C_{1-6} alkyl;

SOR^{18}, SO_2R^{19}, C(O)AZ, lower alkyl, lower alkenyl, lower alkynyl, Het, alkylHet, aryl, alkylaryl (which latter seven groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

Y represents C or S(O)

A represents lower alkylene

Z represents OR^6, halo, Het or aryl (which latter two groups are both optionally substituted with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

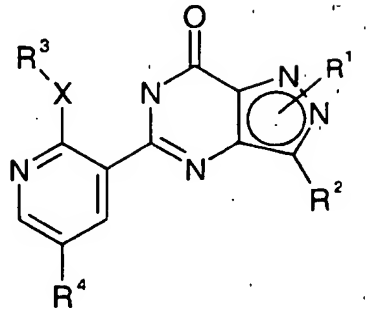
R^{10} and R^{11} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$ and $NR^{20}S(O)_2R^{21}$ or Het or aryl optionally substituted with one or more of said latter thirteen groups) or one of R^{10} and R^{11} may be lower alkoxy, amino or Het, which latter two groups are both optionally substituted with lower alkyl

R^{10a} and R^{11a} independently represent R^{10} and R^{11} as defined above, except that they do not represent groups that include lower alkyl, Het or aryl, when these three groups are substituted and/or terminated (as appropriate) by one or more substituents that include one or more $C(O)NR^{10a}R^{11a}$ and/or $NR^{12}R^{13}$ groups

R^{12} and R^{13} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$), one of R^{12} or R^{13} may be C(O)-lower alkyl or C(O)Het (in which Het is optionally substituted with lower alkyl), or R^{12} and R^{13} together represent C_{3-7} alkylene (which alkylene group is optionally unsaturated, optionally

Claims

1. A compound of general formula I:



I

or a pharmaceutically or veterinarily acceptable salt and/or solvate thereof, wherein

X represents O or NR^5

R^1 represents H, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^2 represents H, halo, cyano, nitro, OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^3 represents H, lower alkyl, alkylHet or alkylaryl (which latter three groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^4 represents H, halo, cyano, nitro, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $NR^{16}Y(O)R^{17}$, $N[Y(O)R^{17}]_2$,

64	7
65	4
71	1
72	0.3
73	5
75	5
76	3
77	0.9
78	0.3
79	1.6
80	0.9
81	2
82	4
83	2
84	7.5

Example 143

5-[2-Isobutoxy-5-(methylsulfonyl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of example 142 (36 mg, 0.09 mmol) in ice-cold methylene chloride (3 ml) was treated with 3-chloroperbenzoic acid (36 mg, 50% pure, 0.09 mmol) and stirred for 2h with ice-cooling. The reaction mixture was diluted with methylene chloride (20 ml) washed with sodium carbonate (10% aq., 2 x 20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated to afford the title compound as a white solid (37 mg, 0.09 mmol).

1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (3H, t), 1.1 (6H, d), 1.75-1.9 (2H, m), 2.25-2.4 (1H, m), 3.0 (2H, t), 3.2 (3H, s), 4.1 (3H, s), 4.5 (2H, d), 8.8 (1H, d), 9.2 (1H, d), 10.6 (1H, br s).

LRMS (TSP) 420 (MH^+).

Biological Activity

Compounds of the invention were found to have *in vitro* activities as inhibitors of cGMP PDE5 with IC_{50} values of less than about 100 nM.

The following Table illustrates the *in vitro* activities for a range of compounds of the invention as inhibitors of cGMP PDE5.

Example	IC_{50} (nM)
5	8.5
16	6.55
34	30.7
48	2.45
49	18
59	1.41

The title compound of example 141 (500 mg, 1.07 mmol) and thiourea (90 mg, 1.18 mmol) were suspended in *N,N*-dimethylformamide (3 ml), degassed at 70°C, and treated with bis(triethylphosphine) nickel (II) chloride (20 mg, 0.05 mmol). Sodium cyanoborohydride (80 µl of 1M solution in THF, 0.08 mmol) was added, and the resultant black reaction mixture heated for ¾ h before further bis(triethylphosphine) nickel (II) chloride (60 mg, 0.16 mmol) and sodium cyanoborohydride (160 µl of 1M solution in THF, 0.16 mmol) were added and the reaction mixture heated for a further 6 h. The green reaction mixture was allowed to cool to room temperature and calcium oxide (90 mg, 1.6 mmol) added. After 1 h, methyl iodide (150 ?l, 2.4 mmol) was added and the mixture stirred for a further 1h. The reaction mixture was diluted with ethyl acetate (20 ml) and citric acid (10% aq, 20ml), the organic phase separated and washed with further citric acid (2 x 20 ml), brine (20 ml) and dried ($MgSO_4$) to afford crude 5-[2-isobutoxy-5-(methylsulfanyl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.

The crude sulphide (284 mg, assume 0.73 mmol) was dissolved in ice-cold methylene chloride (4 ml) and isopropyl alcohol (1 ml), treated with 3-chloroperbenzoic acid (230 mg of 55% active, 0.73 mmol) and allowed to stir at 0°C for 1h after which the solvent was removed *in vacuo.* The residue taken up in ethyl acetate (20 ml), washed with sodium carbonate (10% aq, 2 x 5 ml), brine (5 ml) and dried ($MgSO_4$) before condensing to a solid which was purified by column chromatography (ethyl acetate: pentane 1:1 to ethyl acetate, then ethyl acetate : methanol 99:1) to afford an analytical sample of the title compound (50 mg, 0.13 mmol) together with impure sulphoxide (66 mg, 0.16 mmol).

1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (3H, t), 1.1 (6H, d), 1.75-1.85 (2H, m), 2.25-2.35 (1H, m), 2.8 (3H, s), 3.0 (2H, t), 4.1 (3H, s), 4.4 (2H, d), 8.5 (1H, s), 9.0 (1H, s), 10.7(1H, br s).

LRMS (TSP) 404 (MH^+), 426 (MNa^+).

3H), 3.9 (t, 2H), 3.9-4.0 (m, 1H), 4.1-4.2 (m, 1H), 4.45 (t, 2H), 4.55 (t, 2H), 4.95 (app t, 1H), 8.25 (d, 1H), 8.65 (d, 1H), 10.8 (br s, 1H).

LRMS (TSP) 442 (MH^+), 464 (MNa^+).

Example 140

5-[5-Acetyl-2-(2-methoxyethoxy)-3-pyridinyl]-3-[6-(dimethylamino)-3-pyridinyl]-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of example 59 *via* the method of example 132 using 2-methoxyethanol in 28% yield (25mg).

1H NMR (400 MHz, $CDCl_3$): δ = 2.6 (s, 3H), 3.2 (s, 6H), 3.58 (s, 3H), 3.87 (t, 2H), 4.18 (s, 3H), 4.8 (t, 2H), 6.7 (d, 1H), 7.8 (d, 1H), 8.45 (s, 1H), 8.83 (s, 1H), 9.15 (s, 1H), 10.9 (br s, 1H).

LRMS (TSP) 464 (MH^+).

Example 141

5-(5-Iodo-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of preparation 64 using the method of example 1 and isobutanol as solvent.

1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (3H, t), 1.1 (6H, d), 1.75-1.9 (2H, m), 2.2-2.35 (1H, m), 3.0(2H, t), 4.1 (3H, s), 4.35 (2H, d), 8.4 (1H, s), 8.95 (1H, s).

Analysis: Found C, 46.1; H, 4.70; N, 14.85. Calcd for $C_{18}H_{22}N_5O_2I$: C, 46.26; H, 4.75; N, 14.99%

Example 142

5-[2-Isobutoxy-5-(methylsulfinyl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

4.50 (m, 1H), 4.58 (t, 2H), 4.83 (m, 1H), 5.03 (m, 1H), 8.27 (s, 1H), 8.86 (s, 1H), 10.84 (br s, 1H).

LRMS (TSP - positive) 483.8 (MH^+)

Example 138

5-(5-Acetyl-2-ethoxy-3-pyridinyl)-3-ethyl-1-[(1-methyl-1H-imidazol-2-yl)methyl]-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound was prepared by the method of example 128 from the title compound of preparation 63.

mpt. 217.9-218.7°C

1H NMR (400MHz, $CDCl_3$): δ = 1.18 (t, 3H), 1.58 (t, 3H), 2.61 (s, 3H), 2.95 (q, 2H), 3.75 (s, 3H), 4.70 (q, 2H), 5.83 (s, 2H), 6.80 (s, 1H), 6.98 (s, 1H), 8.81 (s, 1H), 9.25 (s, 1H), 10.88 (br s, 1H)

LRMS (TSP - positive) 422 (MH^+)

Anal. Found C, 59.50; H, 5.46; N, 23.11. Calcd for $C_{21}H_{23}O_3N_7$: C, 59.85; H, 5.50; N, 23.26.

Example 139

5-(2-Butoxy-5-tetrahydro-2-furanyl-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

A solution of the title compound from example 12 (50 mg, 0.11 mmol) in ethanol (10 ml) was charged with 10% Pd on carbon (15 mg) and stirred at room temperature for 6h under 60 psi of hydrogen. After removal of the catalyst by filtration, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (eluting with methylene chloride to 98:2 methylene chloride:methanol) to afford the title compound as a white solid after precipitation from diethyl ether (15 mg, 0.03 mmol).

1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.4 (t, 3H), 1.45-1.6 (m, 2H), 1.8-1.95 (m, 3H), 2.0-2.1 (m, 2H), 2.3-2.4 (m, 1H), 3.15 (q, 2H), 3.25 (s,

1H), 10.52 (s, 1H)

LRMS (TSP – positive ion) 453 (MH^+)

Anal. Found C, 63.15; H, 7.24; N, 17.90 Calcd for $C_{24}H_{32}O_3N_6.0.3H_20.0.1DIPE$ C, 63.11; H, 7.32; N, 17.95

Example 136

5-(5-Acetyl-2-isobutoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 132 from the title compound of example 120.

1H NMR (400MHz, $CDCl_3$): δ = 1.10 (d, 6H), 1.39 (t, 3H), 2.22-2.37 (m, 1H), 2.50 (s, 3H), 2.62 (s, 3H), 3.05 (q, 2H), 3.89 (t, 2H), 3.95 (t, 2H), 4.45 (d, 2H), 5.14 (m, 1H), 8.83 (s, 1H), 9.22 (s, 1H), 10.62 (br s, 1H)

LRMS (TSP – positive ion) 425.5(MH^+)

Example 137

2-(1-Acetyl-4-piperidinyl)-5-[2-butoxy-5-(1-hydroxyethyl)-3-pyridinyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Sodium borohydride (6 mg, 0.15 mmol) was added to a suspension of the title compound from example 131 (140 mg, 0.3mmol) in dry methanol (3 ml) at 0°C under nitrogen. After 30 min the solvent was removed *in vacuo*, and the residue partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was separated, and the aqueous layer was extracted further with ethyl acetate (2 x 20 ml). Combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (98:2 to 95:5 methylene chloride:methanol as eluent) to yield the title compound as a white foam (120 mg, 0.25 mmol).

1H NMR (300MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.54 (m, 2H), 1.60 (d, 3H), 1.91 (m, 2H), 2.01 (t, 2H), 2.13 (m, 1H), 2.17 (s, 3H), 2.32 (m, 1H), 2.59 (m, 1H), 2.78 (t, 1H), 3.08 (q, 2H), 3.28 (t, 1H), 4.08 (m, 1H),

1H NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.35 (t, 3H), 1.50-1.60 (m, 2H), 1.90-2.00 (m, 2H), 2.60 (s, 3H), 3.05 (q, 2H), 4.60 (t, 2H), 5.65 (s, 2H), 7.10 (d, 1H), 7.20 (m, 1H), 7.60 (dd, 1H), 8.60 (d, 1H), 8.85 (s, 1H), 9.25 (s, 1H), 11.65 (s, 1H)

LRMS (TSP – positive ion) 447 (MH^+)

Anal. Found C, 63.73; H, 5.91; N, 18.02. Calcd for $C_{24}H_{26}O_3N_6.0.25H_2O.0.1EtOAc$: C, 63.74; H, 5.98; N, 18.28.

Example 134

5-(5-Acetyl-2-isobutoxy-3-pyridinyl)-3-ethyl-2-(2-pyridinylmethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of example 116 by the method of example 132.

1H NMR (400MHz; $CDCl_3$): δ = 1.10 (d, 6H), 1.30 (t, 3H), 2.30 (m, 1H), 2.60 (s, 3H), 3.00 (q, 2H), 4.45 (d, 2H), 5.65 (s, 2H), 7.10 (d, 1H), 7.25 (m, 1H), 7.60 (dd, 1H), 8.60 (d, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.70 (s, 1H)

LRMS (TSP – positive ion) 447 (MH^+)

Anal. Found C, 62.47; H, 5.87; N, 16.70. Calcd for $C_{24}H_{26}O_3N_6.0.5H_2O.0.5EtOAc$: C, 62.51; H, 6.25; N, 16.82.

Example 135

5-(5-Acetyl-2-isobutoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of example 125 following the method of example 132.

m.p. 195.0-196.0°C

1H NMR (300MHz, $CDCl_3$): δ = 1.08 (d, 6H), 1.38 (t, 3H), 1.88 (d, 2H), 2.10 (t, 2H), 2.20-2.30 (m, 1H), 2.30 (s, 3H), 2.50 (q, 2H), 2.62 (s, 3H), 2.88-3.05 (m, 4H), 4.17-4.23 (m, 1H), 4.41 (d, 2H), 8.80 (s, 1H), 9.19 (s,

.0.2CH_2Cl_2: C, 60.18; H, 6.61; N, 16.71.

Example 132

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from example 119 (120 mg, 0.28 mmol) and cesium carbonate (274 mg, 0.84 mmol) were dissolved in *n*-butanol (4 ml), and heated at 90°C under nitrogen with molecular sieves for 96h. The mixture was then partitioned between water (10 ml) and dichloromethane (10 ml). The organic layer was separated, and the aqueous layer extracted further with dichloromethane (3 x 15 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (95:5:0.5-90:10:1 ethyl acetate:methanol:0.88 NH_3 as eluents), to yield the title compound as a colourless glass (77 mg, 0.18 mmol).

m.p. 91.6-93.7°C

1H NMR (400MHz, $CDCl_3$): δ = 1.00-1.05 (m, 6H), 1.38 (t, 3H), 1.50-1.62 (m, 2H), 1.90-2.00 (m, 2H), 2.63 (s, 3H), 2.63-2.70 (m, 2H), 3.02 (q, 2H), 3.75 (t, 2H), 3.90 (t, 2H), 4.68 (t, 2H), 5.10-5.20 (m, 1H), 8.84 (s, 1H), 9.23 (s, 1H), 10.63 (br s, 1H).

LRMS (TSP – positive ion) 439 (MH^+)

Anal. Found C, 60.73; H, 7.06; N, 18.03 Calcd for $C_{23}H_{30}O_3N_6$.0.2MeOH.0.1 DIPE: C, 60.88; H, 7.26; N, 17.90

Example 133

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(2-pyridinylmethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of example 116 by the method of example 132.

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Trifluoroacetic acid (7 ml, 40%vol) was added to a solution of the title compound of example 129 in dry Methylene chloride (10 ml), and the mixture was stirred at room temperature under nitrogen for 45 mins. The mixture was concentrated *in vacuo* and the residue partitioned between $NaHCO_3$ (sat. aq., 50 ml) and Methylene chloride (100 ml). The organic layer was separated (emulsion) and washed with water (50 ml). Organic layer was removed, and the aqueous extracted with Methylene chloride (2 x 50 ml). The combined organics were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by column chromatography (95:5:0.5 methylene chloride:methanol:0.88 NH_3 as eluent) to yield the title compound (containing trace impurity; carried through crude to next step).

1H NMR (400MHz, $CDCl_3$): δ = 0.98 (t, 3H), 1.39 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 1.92 (m, 2H), 2.15 (m, 2H), 2.61 (s, 3H), 2.81 (m, 2H), 3.03 (q, 2H), 3.32 (m, 2H), 4.39 (m, 1H), 4.62 (t, 2H), 8.80 (s, 1H), 9.19 (s, 1H)

LRMS (TSP - positive) 439 (MH^+)

Example 131

5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-(1-acetyl-4-piperidinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared following the method of example 121 from the title compound of example 130.

m.p. 156-157°C

1H NMR (400MHz, $CDCl_3$): δ = 0.98 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.89 (m, 2H), 1.98 (t, 2H), 2.11 (s, 3H), 2.29 (m, 1H), 2.52 (m, 1H), 2.61 (s, 3H), 2.73 (t, 1H), 3.06 (q, 2H), 3.23 (m, 1H), 4.02 (m, 1H), 4.46 (m, 1H), 4.62 (t, 2H), 4.79 (m, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.57 (br s, 1H).

LRMS (TSP - positive) 481 (MH^+)

Anal. Found C, 60.21; H, 6.58; N, 16.68. Calcd for $C_{25}H_{32}O_4N_6.0.3H_20$

1.42 (t, 3H), 1.52 (t, 3H), 2.61 (s, 3H), 3.03 (q, 2H), 4.18 (d, 2H), 4.71 (q, 2H), 8.81 (s, 1H), 9.22 (s, 1H), 10.59 (br s, 1H).

LRMS (ES - positive) 382 (MH^+)

Anal. Found C, 59.89; H, 5.80; N, 17.01. Calcd for $C_{20}H_{23}O_3N_5.0.3CH_2Cl_2$: C, 59.92; H, 5.85; N, 17.21.

Example 129

tert-Butyl 4-[5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-piperidinecarboxylate

The title compound from preparation 62 (3.70 g, 7.00 mmol) and cesium carbonate (6.84 g, 21.0 mmol) were dissolved in *n*-butanol (60 ml) in the presence of powdered molecular sieves and refluxed under nitrogen for 2h. After removal of the solvent *in vacuo*, the mixture was partitioned between ethyl acetate (100 ml) and water (50 ml). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). Combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the crude product purified by flash column chromatography (99:1 methylene chloride:methanol as eluant). Addition of diethyl ether gave the title compound as a white powder (1.55 g, 2.88 mmol).

m.p. 194-195°C

1H NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.42 (t, 3H), 1.49 (s, 9H), 1.52 (m, 2H), 1.92 (m, 4H), 2.40 (m, 2H), 2.63 (s, 3H), 2.90 (m, 2H), 3.07 (q, 2H), 4.38 (m, 2H), 4.40 (m, 1H), 4.66 (t, 2H), 8.84 (s, 1H), 9.22 (s, 1H), 10.60 (br s, 1H)

LRMS (TSP - positive) 539 (MH^+), 439 (MH^+ - BOC)

Anal. Found C, 62.15; H, 7.17; N, 15.53. Calcd for $C_{28}H_{38}O_5N_6$: C, 62.44; H, 7.11; N, 15.60.

Example 130

dichloromethane/ diisopropylether to yield the title compound as a cream solid (48 mg, 0.12 mmol).

m.p. 184-185°C

1H NMR (400MHz, $CDCl_3$): δ = 0.45 (d, 2H), 0.60 (d, 2H), 0.98 (t, 3H), 1.38 (m, 1H), 1.40 (t, 3H), 1.52 (m, 2H), 1.90 (m, 2H), 2.62 (s, 3H), 3.03 (q, 2H), 4.18 (d, 2H), 4.64 (t, 2H), 8.81 (s, 1H), 9.11 (s, 1H), 10.58 (br s, 1H).

LRMS (TSP - positive) 410 (MH^+)

Anal. Found C, 64.28; H, 6.66; N, 17.03. Calcd for $C_{22}H_{27}O_3N_5$: C, 64.53; H, 6.65; N, 17.10.

Example 128

2-[5-(5-Acetyl-2-ethoxy-3-pyridinyl)-2-((cyclopropyl)methyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from preparation 56 (250 mg, 0.63 mmol) and cesium carbonate (612mg, 1.88mmol) were dissolved in ethanol (15 ml) in the presence of powdered molecular sieves, and the mixture was refluxed for 16h under nitrogen. Further cesium carbonate (103 mg, 0.32 mmol) and powdered molecular sieves were then added, and the mixture transferred into a bomb and heated for 6h at 100°C. The mixture was then diluted with ethyl acetate (50 ml), filtered to remove the molecular sieves and concentrated *in vacuo*. The residues was partitioned between dichloromethane (50 ml) and water (50 ml), the organic layer separated, and the aqueous layer extracted further with dichloromethane (2 x 30 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (99:1 methylene chloride:methanol; then 1:1 ethyl acetate:pentane as eluents), to yield the title compound as a cream solid (45 mg, 0.12 mmol).

m.p. 200-201°C

1H NMR (400MHz, $CDCl_3$): δ = 0.45 (d, 2H), 0.60 (m, 2H), 1.39 (m, 1H),

LRMS (TSP – positive ion) 439 (MH^+)

Anal. Found C, 61.68; H, 6.72; N, 18.61 Calcd for $C_{23}H_{30}O_3N_6.0.2H_20$. 0.1DCM, C, 61.57; H, 6.84; N, 18.65

Example 126

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 51 using the title compound of example 118 and acetaldehyde.

1H NMR (400MHz, $CDCl_3$): δ = 1.05-1.15 (m, 6H), 1.39 (t, 3H), 1.90-2.00 (m, 5H), 2.07-2.22 (m, 1H), 2.42-2.58 (m, 4H), 2.62 (s, 3H), 3.00-3.10 (m, 3H), 3.10-3.20 (m, 1H), 4.20-4.32 (m, 1H), 4.60-4.65 (m, 2H), 8.84 (s, 1H), 9.22 (s, 1H), 10.58 (s, 1H)

LRMS (TSP – positive ion) 453 (MH^+)

Anal. Found C, 62.13; H, 7.05; N, 17.65 Calcd for $C_{24}H_{32}O_3N_6.0.2H_20$. 0.1 CH_2Cl_2.0.1CH_3OH, C, 62.13; H, 7.11; N, 17.96

Example 127

2-[5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-(cyclopropylmethyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from preparation 56 (240 mg, 0.60 mmol) and cesium carbonate (587 mg, 1.80 mmol) were dissolved in *n*-butanol (12 ml), and the mixture was refluxed for 5h under nitrogen. The *n*-butanol was removed *in vacuo*, and the residue partitioned between dichloromethane (30 ml) and water (30 ml). The organic layer was separated, and the aqueous extracted with dichloromethane (2 x 30 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (99:1 methylene chloride:methanol as eluent), and then recrystallised from

2.41 (m, 1H), 2.61 (s, 3H), 2.99 (q, 2H), 3.67-3.74 (m, 2H), 3.85 (t, 2H), 4.59 (t, 2H), 5.06-5.13 (m, 1H), 8.81 (s, 1H), 9.19 (s, 1H), 10.60 (br s, 1H)

LRMS (TSP – positive ion) 453 (MH^+)

Anal. Found C, 60.03; H, 6.93; N, 17.14 Calcd for $C_{24}H_{32}O_3N_6.0.4H_2O.0.3CH_2Cl_2$: C, 60.15; H, 6.94; N, 17.32

Example 124

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 51 using the title compound of example 117 and acetone.

m.p. 162.8-163.6°C

1H NMR (400MHz, MeOD): δ = 1.00 (app. d, 9H), 1.30 (t, 3H), 1.84 (app. q, 2H), 2.60 (s, 3H), 2.62-2.72 (m, 1H), 3.00-3.10 (q, 2H), 3.75 (t, 2H), 3.90 (t, 2H), 4.50 (t, 2H), 5.25 (t, 1H), 8.70 (s, 1H), 8.90 (s, 1H)

LRMS (TSP – positive ion) 439 (MH^+)

Anal. Found C, 61.92; H, 6.84; N, 18.70 Calcd for $C_{23}H_{30}O_3N_6.0.1CH_2Cl_2$: C, 62.07; H, 6.81; N, 18.80

Example 125

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 51 using the title compound of example 118.

m.p. 219.0-220.0°C

1H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.38 (t, 3H), 2.85-2.95 (m, 4H), 2.05-2.15 (m, 2H), 2.30 (s, 3H), 2.50 (q, 2H), 2.62 (s, 3H), 3.00-3.05 (m, 4H), 4.15-4.25 (m, 1H), 4.59 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.55 (s, 1H)

2.62 (s, 3H), 3.02 (q, 2H), 4.46 (d, 2H), 4.56 (dd, 1H), 4.60 (dd, 2H), 5.00-5.10 (m, 1H), 5.26-5.40 (m, 1H), 8.82 (s, 1H), 9.22 (s, 1H), 10.70 (br s, 1H)

LRMS (TSP – positive ion) 439 (MH^+), 456 (MNH_4^+)

Anal. Found C, 56.56; H, 5.82; N, 17.46 Calcd for $C_{22}H_{26}O_4N_6.0.45CH_2Cl_2$: C, 56.56; H, 5.69; N, 17.63

Example 122

2-(1-acetyl-4-piperidinyl)-5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 121 from the title compound of example 118.

m.p. 213-214°C

1H NMR (400MHz, $CDCl_3$): δ = 1.19 (t, 3H), 1.40 (t, 3H), 1.90-2.02 (m, 4H), 2.17 (s, 3H), 2.25-2.38 (m, 1H), 2.50-2.60 (m, 1H), 2.65 (s, 3H), 2.70-2.80 (m, 1H), 3.08 (q, 2H), 3.21-3.30 (m, 1H), 4.01-4.10 (m, 1H), 4.45-4.52 (m, 1H), 4.60 (t, 2H), 4.78-4.85 (m, 1H), 8.84 (s, 1H), 9.22 (s, 1H), 10.64 (s, 1H)

LRMS (TSP – positive ion) 467 (MH^+), 484 (MNH_4^+), 489 (MNa^+)

Anal. Found C, 59.67; H, 6.37; N, 17.15 Calcd for $C_{24}H_{30}O_4N_6.0.4H_20.0.15CH_2Cl_2$, C, 59.62; H, 6.44; N, 17.27

Example 123

5-(5-Acetyl-2-propoxy-3-pyridinyl)-2-(1-*sec*-butyl-3-azetidinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 51 using the title compound of example 117 and but-2-one.

m.p. 176.5-177.7°C

1H NMR (400MHz, $CDCl_3$): δ = 0.85 (t, 3H), 0.93 (d, 3H), 1.06 (t, 3H), 1.11-1.18 (m, 1H), 1.32 (t, 3H), 1.46-1.55 (m, 1H), 1.89-1.98 (m, 2H), 2.36-

LRMS (TSP – positive ion) 426 (MH^+)

Example 120

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 51 using the title compound of example 117.

m.p. 175.9-177.0°C

1H NMR (400MHz, $CDCl_3$): δ = 1.11 (t, 3H), 1.36 (t, 3H), 1.97 (app. q, 2H), 2.50 (s, 3H), 2.65 (s, 3H), 3.02 (q, 2H), 3.79 (t, 2H), 3.92 (dd, 2H), 4.64 (dd, 2H), 5.09-5.19 (m, 1H), 8.85 (d, 1H), 9.23 (d, 1H), 10.65 (br s, 1H)

LRMS (TSP – positive ion) 411.6 (MH^+)

Anal. Found C, 59.70; H, 6.46; N, 19.81 Calcd for $C_{21}H_{26}O_3N_6.0.7H_2O$: C, 59.62; H, 6.53; N, 19.86.

Example 121

2-(1-Acetyl-3-azetidinyl)-5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of example 117 (100 mg, 0.25 mmol) was dissolved in methylene chloride (15 ml). Pyridine (20 ?l, 0.25 mmol) and acetic anhydride (24 ?l, 0.25 mmol) were added and the mixture stirred at room temperature for 1h, poured into water (20 ml), the organic phase separated and the aqueous phase extracted into methylene chloride (2 x 20 ml). Combined organics were washed with HCl (1N, 10 ml), dried over $MgSO_4$, condensed *in vacuo,* and purified by column chromatography (90:10:1 methylene chloride:methanol:ammonia as eluent) to afford the title compound as a white solid (48 mg, 0.11 mmol).

m.p. 229.3-230.1°C

1H NMR (400MHz, $CDCl_3$): δ = 1.1 (t, 3H), 1.38 (t, 3H), 1.90-2.08 (m, 5H),

Example 118

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 117, using the title compound of example 112.

1H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.40 (t, 3H), 1.90-1.99 (m, 4H), 2.30-2.40 (m, 2H), 2.65 (s, 3H), 2.80 (t, 2H), 3.08 (q, 2H), 3.32 (app d, 2H), 4.35-4.40 (m, 1H), 4.62 (app t, 2H), 8.85 (s, 1H), 9.25 (s, 1H)

LRMS (TSP – positive ion) 425 (MH^+)

Anal. Found C, 51.36; H, 5.91; N, 15.18 Calcd for $C_{22}H_{28}O_3N_6.1.45DCM$, C, 51.43; H, 5.69; N, 15.35

Example 119

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Sodium cyanoborohydride (92 mg, 1.47 mmol) was added to a stirring solution of title compound from example 117 (500 mg, 0.98 mmol) and sodium acetate (161 mg, 1.96 mmol) in methanol (10 ml) under nitrogen at room temperature. After 1h the mixture was poured into $NaHCO_3$ (sat. aq., 20 ml), and extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (95:5:0.5-80:20:1 ethyl acetate:methanol:0.88 NH_3 as eluent) to yield the title compound as a white solid (140 mg, 0.33 mmol).

1H NMR (400MHz, $CDCl_3$): δ = 0.97 (t, 3H), 1.03 (t, 3H), 1.30 (t, 3H), 2.82-2.97 (m, 2H), 2.58-2.65 (m, 5H), 2.98 (q, 2H), 3.68 (t, 2H), 3.85 (dd, 2H), 4.58 (dd, 2H), 5.05-5.17 (m, 1H), 8.79 (s, 1H), 9.18 (s, 1H), 10.62 (br s, 1H).

7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Prepared from the title compound of example 110 by the method of example 16.

1H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.30 (t, 3H), 1.95 (m, 2H), 2.60 (s, 3H), 3.00 (q, 2H), 4.60 (t, 2H), 5.70 (s, 2H), 7.10 (d, 1H), 7.20 (d, 1H), 7.65 (t, 1H), 8.60 (d, 1H), 8.85 (s, 1H), 9.25 (s, 1H), 10.70 (s, 1H)

LRMS (TSP – positive ion) 433.4 (MH^+)

Anal. Found C, 58.21; H, 5.52; N, 17.18. Calcd for $C_{23}H_{24}O_3N_6.0.5H_2O.0.5DCM$: C, 58.32; H, 5.42; N, 17.37.

Example 117

5-(5-Acetyl-2-propoxy-3-pyridinyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of example 111 (1.44 g, 3.0 mmol) in acetone (50 ml) and sulphuric acid (1N, 3 ml) was treated with mercuric sulphate (268 mg, 9.0 mmol) and heated to reflux for 6h. The reaction mixture was concentrated to ~20 ml *in vacuo*, poured into sodium bicarbonate (sat. aq., 20ml) and extracted into methylene chloride (6 x 20 ml). Combined organics were washed with brine (20 ml), dried over $MgSO_4$, and concentrated to a brown oil which was taken up in 40% trifluoroacetic acid in methylene chloride (50ml) and water (1 ml) and stirred for 1h at room temperature. After evaporation *in vacuo*, the residue was purified by column chromatography (eluting with 95:5:1 methylene chloride:methanol:0.88 ammonia) to afford the title compound as a white hydroscopic foam (1.65 g).

m.p. 128.5-130.0°C

1H NMR (400MHz, MeOD): δ = 1.00 (t, 3H), 1.30 (t, 3H), 1.79-1.90 (m, 2H), 2.60 (s, 3H), 3.00-3.10 (q, 2H), 4.50 (t, 2H), 4.60-4.70 (m, 4H), 5.65-5.78 (m, 1H), 8.65 (s, 1H), 8.90 (s, 1H)

LRMS (TSP – positive ion) 397 (MH^+)

4H), 4.65 (t, 2H), 4.75 (t, 2H), 8.85 (s, 1H), 9.3 (s, 1H), 10.9 (br s, 1H).

LRMS (ES – negative ion) 453 $(M-H)^-$. (ES – positive ion) 455 (MH^+).

Analysis: found C, 60.43; H, 6.66; N, 18.22. Calcd for $C_{23}H_{30}N_6O_4 \cdot 0.15H_2O$: C, 60.43; H, 6.68; N, 18.38%

Example 114

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 16 from the title compound of example 108 in 73% yield (0.32 mmol).

1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, 3H), 1.42 (t, 3H), 1.5-1.63 (m, 2H), 1.9-2.0 (m, 2H), 2.45-2.58 (m, 4H), 2.65 (s, 3H), 2.87 (t, 2H), 3.0 (q, 2H), 3.55-3.68 (m, 4H), 4.62-4.75 (m, 4H), 8.85 (s, 1H), 9.3 (s, 1H), 10.88 (br s, 1H).

LRMS (EI – positive ion) 469 (MH^+).

Example 115

4-{[5-(5-Acetyl-2-ethoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]methyl}benzonitrile

Using the method of example 16, the title compound was prepared from the title compound of example 109 in 65% yield (110 mg)

1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 1.55 (t, 3H), 2.65 (s, 3H), 2.95 (q, 2H), 4.75 (q, 2H), 5.6 (s, 2H), 7.3 (d, 2H), 7.65 (d, 2H), 8.85 (d, 1H), 9.25 (d, 1H), 10.7 (br s, 1H).

LRMS (TSP) 443 (MH^+), 465 (MNa^+).

Example 116

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(2-pyridinylmethyl)-2,6-dihydro-

Example 111

tert-Butyl 3-[3-ethyl-5-(5-ethynyl-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-azetidinecarboxylate

Prepared from the title compound of example 105 by the method of example 15.

1H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.30 (t, 3H), 1.43 (s, 9H), 1.88-2.00 (m, 2H), 3.00 (q, 2H), 3.19 (s, 1H), 4.35 (app t, 2H), 4.52 (app t, 2H), 4.60-4.80 (br s, 2H), 5.22 (t, 1H), 8.39 (s, 1H), 8.80 (s, 1H), 10.75 (br s, 1H)

LRMS (TSP – positive ion) 496 (MNH_4^+).

Example 112

tert-Butyl 4-[3-ethyl-5-(5-ethynyl-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-piperidinecarboxylate

Prepared from the title compound of example 106 by the method of example 15.

m.p. 221°C

1H NMR (400MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.40 (t, 3H), 1.45 (s, 9H), 1.92 (m, 4H), 2.40 (m, 2H), 2.90 (m, 2H), 3.05 (q, 2H), 3.19 (s, 1H), 4.38 (m, 3H), 4.57 (t, 2H), 8.39 (s, 1H), 8.82 (s, 1H), 10.70 (s, 1H)

LRMS (TSP – positive ion) 507 (MH^+), 524 (MNH_4^+)

Example 113

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Prepared by the method of example 16 from the product of example 107.

m.p. 140-143°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, 3H), 1.4 (t, 3H), 1.95-2.05 (m, 2H), 2.5-2.55 (m, 4H), 2.7 (s, 3H), 2.85-2.95 (m, 2H), 3.0 (q, 2H), 3.6-3.65 (m,

1H NMR (400 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.4 (t, 3H), 1.5-1.6 (m, 2H), 1.9 (tt, 2H), 2.5-2.55 (m, 4H), 2.85 (t, 2H), 2.95-3.05 (m, 2H), 3.6-3.65 (4H, m), 4.6 (t, 2H), 4.7 (t, 2H), 8.0 (s, 1H), 8.4 (s, 1H), 8.85 (s, 1H), 10.95 (br s, 1H).

LRMS (TSP) 451 (MH^+).

Example 109

*4-{[5-(2-Ethoxy-5-ethynyl-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-*d*]pyrimidin-2-yl]methyl}benzonitrile*

The title compound was prepared by the method of example 15 from example 103 in 79% (147 mg).

1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3H), 1.55 (t, 3H), 2.93 (q, 2H), 3.18 (s, 1H), 4.68 (q, 2H), 5.61 (s, 2H), 7.31 (d, 2H), 7.63 (d, 2H), 8.40 (d, 1H), 8.82 (d, 1H), 10.83 (s, 1H).

Example 110

3-Ethyl-5-(5-ethynyl-2-propoxy-3-pyridinyl)-2-(2-pyridinylmethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of example 104 by the method of example 15.

m.p. 189°C

1H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.25 (t, 3H), 1.95 (q, 2H), 3.05 (q, 2H), 3.20 (s, 1H), 4.60 (t, 2H), 5.65 (s, 2H), 7.10 (d, 1H), 7.20 (d, 1H), 7.60 (dd, 1H), 8.40 (s, 1H), 8.60 (d, 1H), 8.80 (s, 1H), 10.80 (s, 1H)

LRMS (TSP – positive ion) 415 (MH^+)

Anal. Found C, 65.05; H, 5.46; N, 19.16. Calcd for $C_{23}H_{22}O_2N_6.0.7H_2O$: C, 64.68; H, 5.52; N, 19.68

pyridinyl]-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)-1-piperidinecarboxylate

Prepared from the title compound of example 100 by the method of example 14.

1H NMR (400MHz, $CDCl_3$): δ = 0.28 (s, 9H), 1.05 (t, 3H), 1.40 (t, 3H), 1.48 (s, 9H), 1.92 (m, 4H), 2.40 (m, 2H), 2.90 (m, 2H), 3.05 (q, 2H), 4.38 (m, 3H), 4.55 (t, 2H), 8.35 (s, 1H), 8.75 (s, 1H), 10.70 (s, 1H)

LRMS (TSP – positive ion) 580 (MH^+), 479 (MH^+ - BOC)

Anal. Found C, 61.86; H, 7.24; N, 14.30 Calcd for $C_{30}H_{42}O_4N_6Si.0.2H_2O$, C, 61.87; H, 7.34; N, 14.43

Example 107

3-Ethyl-5-(5-ethynyl-2-propoxy-3-pyridinyl)-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Prepared by the method of example 15 from the title compound of example 101.

m.p. 137-139°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, 3H), 1.4 (t, 3H), 1.95-2.05 (m, 2H), 2.45-2.5 (m, 4H), 2. 9 (t, 2H), 3.0 (q, 2H), 3.1 (s, 1H), 3.45-3.65 (m, 4H), 4.55 (t, 2H), 4.7 (t, 2H), 8.4 (s, 1H), 8.9 (s, 1H), 11 (br s, 1H).

LRMS (ES – negative ion) 435 $(M-H)^-$. (ES – positive ion) 437 (MH^+).

Analysis: found C, 62.75; H, 6.47; N, 18.79. Calcd for $C_{23}H_{28}N_6O_4 . 0.2H_2O$: C, 63.79; H, 6.47; N, 19.25%

Example 108

5-(2-Butoxy-5-ethynyl-3-pyridinyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 15 from the title compound of example 102 in 88% yield (543 mg).

2.95 (q, 2H), 4.68 (q, 2H), 5.61 (s, 2H), 7.30 (d, 2H), 7.65 (d, 2H), 8.38 (d, 1H), 8.76 (d, 1H), 10.83 (s, 1H).

Example 104

3-Ethyl-5-{2-propoxy-5-[(trimethylsilyl)ethynyl]-3-pyridinyl}-2-(2-pyridinylmethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Prepared from the title compound of example 98 by the method of example 14.

1H NMR (400MHz, $CDCl_3$): δ = 0.20 (s, 9H), 1.00 (t, 3H), 1.25 (t, 3H), 1.90 (m, 2H), 3.00 (q, 2H), 4.50 (t, 2H), 5.60 (s, 2H), 7.00 (d, 1H), 7.20 (m, 1H), 7.60 (dd, 1H) 8.30 (s, 1H), 8.55 (d, 1H), 8.75 (s, 1H), 10.70 (s, 1H)

LRMS (TSP – positive ion) 487.5 (MH^+)

Example 105

tert-Butyl 3-(3-ethyl-7-oxo-5-{2-propoxy-5-[(trimethylsilyl)ethynyl]-3-pyridinyl}-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)-1-azetidinecarboxylate

Prepared from the title compound of example 99 by the method of example 14.

1H NMR (400MHz, MeOD): δ = 0.25 (s, 9H), 1.05 (t, 3H), 1.31 (t, 3H), 1.44 (s, 9H), 1.87-1.96 (m, 2H), 3.00 (q, 2H), 4.33 (t, 2H), 4.52 (t, 2H), 4.54-4.80 (m, 2H), 5.18-5.25 (m, 1H), 8.32 (d, 1H), 8.74 (d, 1H)

LRMS (TSP – positive ion) 569 (MNH_4^+), 452.0 (MH^+)

Anal. Found C, 60.82; H, 6.90; N, 15.15 Calcd for $C_{28}H_{38}O_4N_6Si$: C, 61.07; H, 6.95; N, 15.26.

Example 106

tert-Butyl 4-(3-ethyl-7-oxo-5-{2-propoxy-5-[(trimethylsilyl)ethynyl]-3-

3-Ethyl-1-[2-(4-morpholinyl)ethyl]-5-{2-propoxy-5-[(trimethylsilyl)ethynyl]-3-pyridinyl}-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Prepared by the method of example 14 from the title compound of example 95.

m.p. 132-134°C.

1H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.1 (t, 3H), 1.4 (t, 3H), 1.95-2.05 (m, 2H), 2.45-2.5 (m, 4H), 2.85 (t, 2H), 3.0 (q, 2H), 3.55-3.65 (m, 4H), 4.55 (t, 2H), 4.7 (t, 2H), 8.35 (s, 1H), 8.8 (s, 1H), 11 (br s, 1H).

LRMS (ES – negative ion) 507 $(M-H)^-$. (ES – positive ion) 509 (MH^+).

Analysis: found C, 61.18; H, 7.12; N, 16.53. Calcd for $C_{26}H_{36}N_6O_3Si$: C, 61.39; H, 7.13; N, 16.52%

Example 102

5-{2-Butoxy-5-[(trimethylsilyl)ethynyl]-3-pyridinyl}-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of example 14 from the title compound of example 96 in 69% yield (550 mg).

1H NMR (400 MHz, $CDCl_3$): δ = 0.38 (s, 9H), 1.02 (t, 3H), 1.42 (t, 3H), 1.5-1.6 (m, 2H), 1.85-1.98 (m, 2H), 2.46-2.56 (m, 4H), 2.85 (t, 2H), 3.0 (q, 2H), 3.55-3.65 (m, 4H), 4.6 (t, 2H), 4.7 (t, 2H), 8.38 (s, 1H), 8.85 (s, 1H), 10.98 (s, 1H).

LRMS (TSP) 524 (MH^+).

Example 103

4-[(5-{2-Ethoxy-5-[(trimethylsilyl)ethynyl]-3-pyridinyl}-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl)methyl]benzonitrile

The title compound was prepared by the method of example 14 from the product of example 97.

1H NMR (300 MHz, $CDCl_3$): δ = 0.27 (s, 9H), 1.30 (t, 3H), 1.54 (t, 3H),

1H), 8.40 (s, 1H), 8.55 (d, 1H), 8.95 (s, 1H), 10.70 (s, 1H)

LRMS (ES – positive ion) 517 (MH^+)

Anal. Found C, 48.73; H, 3.89; N, 16.14. Calcd for $C_{21}H_{21}O_2N_6I$: C, 48.85; H, 4.10; N, 16.28.

Example 99

tert-Butyl 3-[3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-azetidinecarboxylate

The title compound was prepared from the product of preparation 52 using the method of example 95.

1H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.30 (t, 3H), 1.43 (s, 9H), 1.87-1.96 (m, 2H), 3.00 (q, 2H), 4.34 (t, 2H), 4.49 (t, 2H), 4.60 (br s, 2H), 5.20 (t, 1H), 8.41 (d, 1H), 8.94 (s, 1H), 10.75 (br s, 1H)

LRMS (TSP – positive ion) 598.1 (MNH_4^+)

Anal. Found C, 47.54; H, 5.02; N, 14.09 Calcd for $C_{23}H_{29}O_4N_6I$: C, 47.60; H, 5.04; N, 14.48.

Example 100

tert-Butyl 4-[3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-piperidinecarboxylate

The title compound was prepared from the product of preparation 53 using the method of example 95.

1H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 1.40 (t, 3H), 1.45 (s, 9H), 1.92 (m, 4H), 2.40 (m, 2H), 2.90 (m, 2H), 3.08 (q, 2H), 4.38 (m, 3H), 4.50 (t, 2H), 8.40 (s, 1H), 8.98 (s, 1H), 10.69 (s, 1H)

LRMS (TSP – positive ion) 609.7 (MH^+), 509.0 (MH^+ - BOC)

Example 101

butanol (12 ml) was treated with potassium hexamethyldisilazide (2.18 g, 10.9 mmol) and the reaction mixture heated to reflux for 60h, After removal of the solvent *in vacuo*, the residue was partioned between water and methylene chloride, the pH adjusted to 7 (2N HCl) and the aqueous phase separated, and extracted with methylene chloride. Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to a residue which after trituration with pentane, afforded the title compound (0.84 g, 1.5 mmol).

1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, 3H), 1.4 (t, 3H), 1.5-1.6 (m, 2H), 1.85-1.95 (m, 2H), 2.5-2.6,(m, 4H), 2.85 (t, 2H), 2.97 (q, 2H), 3.6-3.65 (m, 4H), 4.55 (t, 2H), 4.75 (t, 2H), 8.45 (d, 1H), 9.05 (d, 1H), 10.95 (br s, 1H).

Example 97

4-{[5-(2-Ethoxy-5-iodo-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]methyl}benzonitrile

The title compound was prepared from the title compound of preparation 50 in ethanol using the method of example 95.

1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 1.5 (t, 3H), 2.95 (q, 2H), 4.6 (q, 2H), 5.6 (s, 2H), 7.25 (d, 2H), 7.60 (d, 2H), 8.40 (d, 1H), 8.95 (d, 1H), 10.8 (br s, 1H).

LRMS 527 (MH^+), 549 (MNa^+).

Example 98

5-(2-Propoxy-5-iodo-3-pyridinyl)-3-ethyl-2-(2-pyridinylmethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of preparation 51 using the method of example 95.

m.p. 228.9-233.8°C

1H NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.25 (t, 3H), 1.90 (m, 2H), 3.00 (q, 2H), 4.50 (t, 2H), 5.65 (s, 2H), 7.05 (d, 1H), 7.20 (m, 1H), 7.60 (t,

58.86; H, 6.59; N, 19.61%

Example 95

3-Ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of preparation 48 (15.78 g, 28.4 mmol) was dissolved in n-propanol (200 ml), ethyl acetate (6 ml) and potassium t-butoxide (3.2 g, 28.4 mmol) were added and the resultant mixture heated to reflux for 6h. Additional potassium t-butoxide (1.6 g, 14.2 mmol) was added and the mixture heated for a further 2h, after which the solvent was removed *in vacuo*. The residue was partioned between water (50 ml) and methylene chloride (100 ml) and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 x 100 ml) and the combined organics dried over $MgSO_4$ and reduced to a yellow solid (~17 g). Purification by column chromatography (elution with ethyl acetate) gave the title compound (13.3 g, 24.1 mmol) together with recovered starting material (2.31 g, 4.2 mmol).

m.p. 175-177°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.1 (t, 3H), 1.4 (t, 3H), 1.9-2.05 (m, 2H), 2.45-2.55 (m, 4H), 2. 85 (t, 2H), 3.0 (q, 2H), 3.6-3.65 (m, 4H), 4.5 (t, 2H), 4.7 (t, 2H), 8.4 (s, 1H), 9.0 (s, 1H), 10.95 (br s, 1H):

LRMS (TSP) 540 (MH^+).

Analysis: found C, 46.79; H, 5.01; N, 15.44. Calcd for $C_{21}H_{27}N_6O_3I$: C, 46.85; H, 5.05; N, 15.61%

Example 96

5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of preparation 49 (1.25 g, 2.3 mmol) in degassed n-

and concentrated to a residue which was purified by column chromatography (eluting with 1:4 ethyl acetate : pentane) to give the title compound as a yellow solid (24 mg, 0.06 mmol).

m.p. 162-162.5°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.13 (t, 3H), 1.80-2.0 (m, 4H), 2.90 (t, 2H), 2.97 (s, 6H), 4.26 (s, 3H), 4.45 (t, 2H), 5.29 (s, 1H), 7.81 (s, 1H), 8.29 (s, 1H).

LRMS (TSP)371 (MH^+).

Analysis: Found C, 61.46; H, 7.08; N, 22.62. Calcd for $C_{19}H_{26}N_6O_2$: C, 61.60; H, 7.08; N, 22.59%

Example 94

Propyl 5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinylcarbamate

The title compound of preparation 36 (114 mg; 0.23 mmol) in propanol (15 ml) was treated with potassium bis(trimethylsilylamide) (148 mg, 0.92 mmol) and the resultant mixture heated to 80°C for 4.5 h, allowed to cool and concentrated *in vacuo*. The residue was partioned between water (20 ml) and ethyl acetate (20 ml), and the aqueous phase separated and extracted with ethyl acetate (2 x 20 ml). The combined organics were washed with water (20 ml), brine (20 ml) and dried ($MgSO_4$) before concentrating to an off-white solid. Purification by column chromatography (eluting with 3:10 ethyl acetate : pentane) gave the title compound as a white solid (60 mg, 0.14 mmol).

m.p. 210-211°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.03 (t, 3H), 1.13 (t, 3H), 1.65-2.0 (m, 6H), 2.90 (t, 2H), 4.16 (t, 2H), 4.26 (s, 3H), 4.52 (t, 2H), 6.5 (br s, 1H), 7.26 (d, 1H), 8.69 (d, 1H), 11.2 (br s, 1H).

LRMS (TSP) 429 (MH^+).

Analysis: Found C, 58.88; H,6.63; N, 19.61. Calcd for $C_{21}H_{28}N_6O_4$: C,

Example 92

N-[6-(Propoxy)-5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]acetamide

Acetic anhydride (30 ?L, 0.35 mmol) was added to a solution of the title compound of example 74 (100 mg, 0.29 mmol) in THF (1 ml) and the resultant solution stirred at room temperature for 2h. Saturated sodium carbonate (10 ml) and ethyl acetate (10 ml) were added, and the aqueous phase separated and extracted with ethyl acetate (2 x 10 ml). Combined organics were washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$ and condensed to the title compound as a white solid (101 mg, 0.26 mmol).

m.p. 252-3°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, 3H), 1.13 (t, 3H), 1.80-2.0 (m, 4H), 2.23 (s, 3H), 2.90 (t, 2H), 4.26 (s, 3H), 4.52 (t, 2H), 7.13 (br s, 1H), 8.61 (s, 1H), 8.71 (s, 1H), 11.15 (br s, 1H).

LRMS (TSP) 385 (MH^+).

Analysis: Found C, 59.08; H, 6.26; N, 21.45. Calcd for $C_{19}H_{24}N_6O_3$. 0.1 H_2O: C, 59.09; H, 6.32; N, 21.76%

Example 93

5-[5-(Dimethylamino)-2-propoxy-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of example 74 (100 mg, 0.29 mmol) was added to 37% aqueous formaldehyde solution (0.13 ml, 1.74 mmol) and formic acid (0.21 ml, 5.6 mmol), and the resultant mixture heated to 90°C for 24h. After allowing to cool, the reaction mixture was diluted with water (20 ml), neutralised with NaOH (2M) and extracted with ethyl acetate (2 x 20 ml). The combined extracts were washed with water (20 ml), dried over $MgSO_4$

1H), 7.75 (s, 1H), 8.2 (1H, s), 11.3 (br s, 1H).

LRMS (TSP) 355 (MH^+).

Analysis: Found C, 60.73; H, 6.37; N, 22.89. Calcd for $C_{18}H_{22}N_6O_2 . 0.1H_2O$: C, 60.85; H, 6.33; N, 23.14%

N-[6-(cyclobutyloxy)-5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]acetamide:

m.p. 279-281°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.65-1.9 (m, 4H), 2.2 (s, 3H), 2.25-2.3 (m, 2H), 2.5-2.6 (m, 2H), 2.85 (t, 2H), 4.2 (s, 3H), 5.35-5.4 (m, 1H), 7.2 (s, 1H), 8.55 (s, 1H), 8.65 (s, 1H), 11.0 (br s, 1H).

LRMS (TSP) 397 (MH^+).

Example 91

N-[6-(Propoxy)-5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]-*N*,*N*-dimethylurea

Dimethylcarbamoyl chloride (0.03 ml, 0.32 mmol) was added to a solution of the title compound of example 74 (100 mg, 0.29 mmol), 4-dimethylaminopyridine (2 mg), and triethylamine (0.08 ml, 0.58 mmol) in methylene chloride (5ml). The resultant mixture was stirred at room temperature for 10 days, concentrated *in vacuo* and the residue purified by column chromatography (elution with ethyl acetate) to afford the title compound as a white solid (105 mg, 0.25 mmol).

m.p. 219-220°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, 3H), 1.13 (t, 3H), 1.8-1.9 (m, 2H), 1.9-2.0 (m, 2H), 2.90 (t, 2H), 3.06 (s, 6H), 4.26 (s, 3H), 4.52 (t, 2H), 6.26 (br s, 1H), 8.48 (d, 1H), 8.58 (d, 1H), 11.2 (br s, 1H).

LRMS (TSP) 414 (MH^+).

Analysis: Found C, 57.96; H, 6.58; N, 23.65. Calcd for $C_{20}H_{27}N_7O_3$: C, 58.10; H, 6.58; N, 23.71%

Analysis: Found C, 56.03; H, 5.28; N, 21.63. Calcd for $C_{18}H_{20}N_6O_4$: C, 56.24; H, 5.24; N, 21.86%

Example 89

N-[6-(Cyclobutyloxy)-5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]acetamide

and

Example 90

5-[5-Amino-2-(cyclobutyloxy)-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from example 88 (266 mg, 0.69 mmol) was dissolved in glacial acetic acid (10 ml) and the vessel charged with 5% Pd on carbon (20 mg) and stirred under hydrogen (60 psi) for 14h. The catalyst was removed by filtration (Arbocel*) and the residue concentrated *in vacuo*. The residue was taken up in water (5 ml), basified to pH 8 (5% $NaHCO_3$ solution) and extracted with methylene chloride (3 x 20 ml). Combined organic extracts were washed with brine (20 ml), dried over $MgSO_4$, reduced *in vacuo* and purified by column chromatography (first with 98:2 methylene chloride:methanol as eluant, then 30:70:1 ethyl acetate:pentane:0.88 ammonia). 5-[5-amino-2-(cyclobutyloxy)-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one was obtained (70 mg, 0.19 mmol) together with *N*-[6-(cyclobutyloxy)-5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]acetamide (34 mg, 0.09 mmol).

5-[5-amino-2-(cyclobutyloxy)-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one:

m.p. 185-185.5°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.65-2.0 (m, 4H), 2.2-2.35 (m, 2H), 2.5-2.6 (m, 2H), 2.9 (t, 2H), 3.6 (s, 2H), 4.25 (s, 3H), 5.3-5.4 (m,

1.95 mmol) were added followed by *N,O*-dimethylhydroxylamine hydrochloride (173 mg, 1.8 mmol), and the resultant mixture stirred at room temperature for 14 h. Saturated aq. sodium hydrogen carbonate (80 mL) and dichloromethane (50 mL) were added, the organic phase removed and the aqueous phase extracted with dichloromethane (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, concentrated and purified by column chromatography (dichloromethane to 10% methanol in dichloromethane as eluant) to afford the title compound as a yellow oil (590 mg, 1.3 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H), 1.55 (t, 2H), 2.3 (s, 6H), 2.85-2.95 (m, 2H), 3.0 (q, 2H), 3.4 (s, 3H), 3.6 (s, 3H), 4.35-4.45 (m, 2H), 4.7 (q, 2H), 8.7 (s, 1H), 9.2 (s, 1H).

LRMS (TSP) 444 (MH^+).

Example 88

5-[2-(Cyclobutyloxy)-5-nitro-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of preparation 45 (1.0 g, 2.66 mmol), and potassium hexamethyldisilazide (1.72 g, 10.63 mmol) suspended in cyclobutanol (5 ml) and ethyl acetate (0.5 ml) was heated to reflux for 14 h. After cooling, the solvent was removed *in vacuo* and the residue taken up in water (20 ml) and extracted with methylene chloride (3 x 50 ml). Combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$ and concentrated to a yellow solid (~800 mg). Purification by column chromatography (elution with 3:7 ethyl acetate:pentane) gave the title compound (295 mg, 0.76 mmol).

m.p. 212-4°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.75-2.1 (m, 4H), 2.3-2.4 (m, 2H), 2.5-2.7 (m, 2H), 2.95 (t, 2H), 4.3 (s, 3H), 5.5-5.6 (m, 1H), 9.1 (s, 1H), 9.5 (s, 1H), 10.8 (br s, 1H).

LRMS (TSP) 385 (MH^+).

to 75°C under 482.6 kPa (70 psi) of CO for 14 h. After filtration through Arbocel®, the reaction mixture was partitioned between dichloromethane (150 mL) and water (150 mL), and the organic phase separated, dried over $MgSO_4$, and concentrated to an orange oil. Purification by column chromatography (eluting with a gradient of dichloromethane:methanol as eluant (100:0 to 90:10) gave methyl 5-{2-[2-(dimethylamino)-ethyl]-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl}-6-ethoxynicotinate as a slightly impure pale orange solid (1.18 g).

^{1}H NMR (400 MHz, $CDCl_3$): 1.4 (t, 3H), 1.45 (t, 3H), 2.3 (s, 6H), 2.9 (t, 2H), 3.05 (q, 2H), 3.95 (s, 3H), 4.4 (t, 2H), 4.7 (q, 2H), 8.9 (s, 1H), 0.25 (s, 1H)

LRMS (TSP) 415 (MH^+)

The crude methyl ester (1.18 g) was taken up in dioxan (20 mL), treated with aq. sodium hydroxide (2 M, 3.4 mL) and the resultant solution stirred at room temperature for 14 h after which the dioxan was removed *in vacuo*, and the remaining aqueous solution washed with toluene (150 mL), acidified with conc. hydrochloric acid to pH 2, and concentrated to a solid. Trituration with hot ethanol (70 mL) afforded the title compound as a white solid (710 mg, 1.8 mmol).

^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.3 (t, 3H), 1.35 (t, 3H), 2.8 (s, 6H), 3.1 (q, 2H), 3.6-3.7 (m, 2H), 4.4 (q, 2H), 4.75 (t, 2H), 8.4 (s, 1H), 8.8 (s, 1H), 10.5 (br s, 1H), 11.9 (s, 1H).

LRMS (TSP) 401 (MH^+).

Example 87

5-{2-[2-(Dimethylamino)ethyl]-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl}-6-ethoxy-*N*-methoxy-*N*-methylnicotinamide

The title compound of Example 86 (710 mg, 1.8 mmol) was dissolved in dichloromethane (150 mL), 1-hydroxybenzotriazole hydrate (263 mg, 1.95 mmol), *N,N*-diisopropylethylamine (1.26 mL, 7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (374 mg,

which was removed by filtration, and dried *in vacuo* to give the title compound as an off-white solid (180 mg, 0.43 mmol)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.1 (t, 3H), 1.6 (d, 3H), 1.8-2.0 (m, 4H), 2.9 (t, 2H), 4.2 (t, 1H), 4.25 (s, 3H), 4.45 (t, 2H), 7.7 (d, 1H), 8.15 (d, 1H), 11.3 (br s, 1H).

LRMS (ES – negative ion) 413 (M-H), 827 (M_2-H).

Analysis: found C, 57.12; H, 6.23; N, 19.92. Calcd for $C_{20}H_{26}N_6O_4$;0.3H_2O: C, 57.21; H, 6.39; N, 20.02%

Example 85

2-[2-(Dimethylamino)ethyl]-5-(2-ethoxy-5-iodo-3-pyridinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of Preparation 39 (2.1 g, 4.1 mmol) was dissolved in *tert*-butanol (40 mL), the solution degassed, treated with potassium hexamethyldisilazide (2.66 g, 16.4 mmol) and heated to 60°C for 24 h. The resultant mixture was concentrated, and the residue taken up in water (200 mL) and extracted with dichloromethane (3 x 100 mL) and the combined organics dried over $MgSO_4$, concentrated and crystallised from ethyl acetate to afford the title compound as a white solid (1.15 g, 2.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H), 1.5 (t, 3H), 2.3 (t, 6H), 2.9 (t, 2H), 3.0 (q, 2H), 4.4 (t, 2H), 4.6 (q, 2H), 8.4 (s, 1H), 9.0 (s, 1H)

LRMS (TSP) 483 (MH^+)

Example 86

5-{2-[2-(Dimethylamino)ethyl]-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl}-6-ethoxynicotinic acid

The title compound of Example 85 (1.27 g, 2.6 mmol) in methanol (100 mL) was treated with DMSO (5 mL), triethylamine (2.6 mL, 18.4 mmol), 1,3-bis(diphenylphosphino)propane (434 mg, 1 mmol) and palladium(II) acetate (414 mg, 1.8 mmol), and the resultant mixture heated

LRMS (ES – negative ion) 413 (M-H)

Analysis: found C, 57.86; H, 6.32; N, 20.21. Calcd for $C_{20}H_{26}N_6O_4$: C, 57.96; H, 6.32; N, 20.28%

Example 83

Methyl 2-{[5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}propanoate

The title compound of Example 74 (300 mg, 0.9 mmol) and methyl 2-bromopropionate (98 µL, 0.9 mmol) were dissolved in *N,N*-diisopropylethylamine (3 mL) and the resultant mixture stirred at room temperature for 14 h, after which additional methyl 2-bromopropionate (24 µL, 0.2 mmol) was added and the mixture heated to reflux for 6 h. The cooled reaction was concentrated *in vacuo* and the residue purified by column chromatography (pre-absorbed, ethyl acetate : pentane (3:10) as eluant) to afford the title compound as a white solid (258 mg, 0.6 mmol).

m.p. 185-7°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (t, 3H), 1.55 (d, 3H), 1.85-2.0 (m, 4H), 2.9 (t, 2H), 3.75 (s, 3H), 4.1 (t, 1H), 4.3 (s, 3H), 4.45 (t, 2H), 7.7 (d, 1H), 8.15 (d, 1H), 11.4 (br s, 1H).

LRMS (ES – negative ion) 427 (M-H).

Analysis: found C, 58.77; H, 6.62; N, 19.13. Calcd for $C_{21}H_{28}N_6O_4$;0.1EtOAc: C, 58.78; H, 6.64; N, 19.22%

Example 84

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]alanine

The title compound of Example 83 in methanol (5 mL) was treated with a solution of sodium hydroxide (64 mg, 1.6 mmol) in water (2 mL) and the reaction mixture stirred at room temperature for 14 h. After concentration of the reaction mixture *in vacuo*, water (5 mL) was added and the solution acidified with conc. hydrochloric acid (5 drops) to afford a white precipitate,

Example 81

1-Methyl-5-(5-{4-[(4-methylphenyl)sulfonyl]-1-piperazinyl}-2-propoxy-3-pyridinyl)-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

N,N-Bis-(2-chloroethyl)-4-methylbenzenesulfonamide (86 mg, 0.3 mmol) was added to a stirred suspension of the title compound of Example 74 (100 mg, 0.3 mmol) in *N,N*-diisopropylethylamine (0.5 mL), and the mixture heated to reflux. Two further portions of *N,N*-bis-(2-chloroethyl)-4-methylbenzene-sulfonamide (each 86 mg, 0.3 mmol) were added after 3 and 6 h. After a total of 21 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (2.5 mL) and purified by column chromatography (preabsorbed, eluting with a gradient of ethyl acetate:pentane (20:80 to 30:70) to afford the title compound as a yellow solid (119 mg, 0.21 mol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.1 (t, 3H), 1.85-2.0 (m, 4H), 2.45 (s, 3H), 2.9 (t, 2H), 3.25 (br s, 8H), 4.3 (s, 3H), 4.5 (t, 2H), 7.35 (d, 2H), 7.7 (d, 2H), 7.9 (d, 1H), 8.4 (d, 1H), 11.3 (br s, 1H).

LRMS (ES – negative ion) 564 (M-H).

Example 82

Methyl {[5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}acetate

The title compound of Example 74 (200 mg, 0.6 mmol) and methylbromoacetate (55 µL, 0.58 mmol) were dissolved in *N,N*-diisopropylamine (2 mL) and the mixture heated to reflux for 20 h. After cooling, the reaction mixture was pre-absorbed onto silica, and purified by column chromatography (ethyl acetate:pentane (50:50) as eluant) to give the title compound as an off-white solid (139 mg, 0.34 mmol).

m.p. 175°C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.15 (t, 3H), 1.8-1.95 (m, 4H), 2.9 (t, 2H), 3.75 (s, 3H), 3.95 (d, 2H), 4.25 (s, 3H), 4.45 (t, 2H), 7.65 (d, 1H), 8.15 (d, 1H), 11.25 (br s, 1H)

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.9-1.0 (m, 6H), 1.65-1.8 (m, 4H), 2.7-2.85 (m, 2H), 3.35 (s, 2H), 4.15 (s, 3H), 4.25-4.35 (m, 2H), 8.3 (s, 1H), 8.5 (s, 1H), 10.35 (br s, 1H)

LRMS (ES – negative ion) 427 (M-H)

Analysis: found C, 54.32; H, 5.47; N, 18.86. Calcd for $C_{20}H_{24}N_6O_5$;0.75H_2O: C, 54.35; H, 5.82; N, 19.02%

Example 80

({[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}sulfonyl)acetic acid

Chlorosulfonyl chloride (878 mg, 4.6 mmol) in acetonitrile (10 mL) was treated with water (0.08 mL, 4.6 mmol) stirred for 10 min at room temperature, concentrated *in vacuo*, and the residue dissolved in dichloromethane (10 mL). 1.17 mL of this solution was then added dropwise to a stirred solution of the title compound of Example 74 (200 mg, 0.6 mmol) and triethylamine (0.16 mL, 1.2 mmol) in dichloromethane (10 mL). After 14 h, the reaction mixture was extracted with aqueous sodium hydroxide (2 M, 2 x 10 mL) and the combined aqueous extracts acidified to pH 3 with conc. hydrochloric acid, and back-extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*, and the residues purified by column chromatography (eluting with a gradient of dichloromethane:methanol in (95:5 to 80:20) to give the title compound as a cream solid (132 mg, 0.4 mmol).

m.p. 267-270°C

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.9-1.0 (m, 6H), 1.65-1.8 (m, 4H), 2.85 (t, 2H), 3.5 (s, 2H), 4.15 (s, 3H), 4.3 (t, 2H), 8.3 (s, 1H), 8.5 (s, 1H), 10.5 (br s, 1H), 12.0 (br s, 1H)

LRMS (ES – negative ion) 463 (M-H)

LRMS (ES – negative ion) 419 (M-H).

Example 78

Methyl 3-{[5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}-3-oxopropanoate

Methyl malonyl chloride (31 µL, 0.3 mmol) was added dropwise to a stirred solution of the title compound of Example 74 (100 mg, 0.3 mmol) and triethylamine (0.08 mL, 0.6 mmol) in dichloromethane (5 mL). The reaction mixture stirred at room temperature for 24 h, diluted with dichloromethane (5 mL), washed with water (2 x 2.5 mL), dried over $MgSO_4$, and concentrated to an orange/brown solid. Purification by column chromatography (ethyl acetate as eluant) gave the title compound as a white solid (96 mg, 0.22 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (t, 3H), 1.85-2.1 (m, 4H), 2.95 (t, 2H), 3.75 (s, 2H), 3.95 (s, 3H), 4.3 (s, 3H), 4.55 (t, 2H), 8.65 (s, 1H), 8.85 (s, 1H), 9.3 (br s, 1H), 11.15 (br s, 1H).

LRMS (ES – positive ion) 443 (MH^+).

Analysis: found C, 56.88; H, 5.87; N, 18.74. Calcd for $C_{21}H_{26}N_6O_5$: C, 57.00; H, 5.92; N, 18.70%

Example 79

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]-3-oxo-β-alanine

Sodium hydroxide (2 *N*, aq., 1 mL) was added to a solution of the title compound of Example 78 (79 mg, 0.18 mmol) in methanol (10 mL) and the resultant mixture stirred at room temperature for 19 h, concentrated *in vacuo* and the residue dissolved in water (20 mL). After washing with dichloromethane (20 mL), the aqueous phase was acidified to pH 2-3 with 2 M HCl and the resultant white precipitate removed by filtration and dried to afford the title compound (58 mg, 0.14 mmol).

m.p. 261-262°C

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]-*N*-(methylsulfonyl)methanesulfonamide

Methane sulfonyl chloride (0.02 mL, 0.3 mmol) was added to a solution of the title compound of Example 74 (100 mg, 0.3 mmol) and triethylamine (0.08 mL, 0.6 mmol) in dichloromethane (5 mL) and the reaction mixture stirred at room temperature for 6 h. After dilution with dichloromethane (5 mL), the reaction mixture was washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated to a residue. Purification by column chromatography (eluting with a gradient of ethyl acetate:pentane (30:70 to 50:50) to give the title compound as a white solid (97 mg, 0. 2 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.1 (t, 3H), 1.8-1.95 (m, 2H), 2.0-2.2 (m, 2H), 2.9 (t, 2H), 3.5 (s, 6H), 4.25 (s, 3H), 4.6 (t, 2H), 8.25 (d, 1H), 8.75 (d, 1H), 10.9 (br s, 1H).

LRMS (TSP) 499 (MH^+).

Analysis: found C, 45.58; H, 5.16; N, 16.67. Calcd for $C_{19}H_{26}N_6O_6S_2$: C, 45.77; H, 5.26; N, 16.86%

Example 77

N-[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]methanesulfonamide

The title compound of Example 76 (56 mg, 0.1 mmol) was dissolved in propanol (1.4 mL) and aq. KOH solution (1 M, 0.14 mL) and the mixture heated to 45°C for 2.5 h. The reaction mixture was concentrated *in vacuo* and the residue diluted with water (2 mL) and acidified to pH 2-3 with conc. hydrochloric acid to afford a precipitate which was removed by filtration, washed with water and diethyl ether before drying to give the title compound as an off-white solid (26 mg, 0.06 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3H), 1.1 (t, 3H), 1.8-1.95 (m, 2H), 1.9-2.0 (m, 2H), 2.9 (t, 2H), 3.05 (s, 3H), 4.25 (s, 3H), 4.5 (t, 2H), 6.25 (br s, 1H), 8.25 (d, 1H), 8.65 (d, 1H), 11 (br s, 1H).

1:1 ethyl acetate:pentane) was benzyl 5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinylcarbamate (777 mg, 1.6 mmol) and the more polar component (R_f=0.5 in 1:1 ethyl acetate:pentane) was the title compound (0.49 g, 1.4 mmol).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 1.05 (t, 3H), 1.1 (t, 3H), 1.85-2.0 (m, 4H), 2.9 (t, 2H), 3.6 (s, 2H), 4.25 (s, 3H), 4.45 (t, 2H), 7.75 (d, 1H), 8.2 (d, 1H), 11.3 (br s, 1H).

LRMS (TSP) 343 (MH^+).

Example 75

{[5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinyl]amino}acetic acid

A solution of sodium bromoacetate (48 mg, 0.33 mmol) in water (1 mL) was added to the title compound of Example 74 (100 mg, 0.3 mmol) and the mixture heated to reflux for 5 days. A further aliquot of sodium bromoacetate (48 mg, 0.33 mmol) was added and heating continued for a further day. After cooling, the reaction mixture was extracted with ethyl acetate (3 x 2.5 mL) and the combined extracts dried over $MgSO_4$, and purified by column chromatography (dichloromethane: methanol: acetic acid (390:10:1) as eluant) to afford, after trituration from diisopropylether, a yellow solid (16 mg, 0.04 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.1 (t, 3H), 1.8-2.0 (m, 4H), 2.9 (t, 2H), 4.05 (s, 2H), 4.25 (s, 3H), 4.45 (t, 2H), 7.65 (d, 1H), 8.2 (d, 1H), 11.25 (br s, 1H).

LRMS (ES – negative ion) 399 (M-H).

Analysis: found C, 56.61; H, 5.98; N, 20.43. Calcd for $C_{19}H_{24}N_6O_4$ + $0.2H_2O$: C, 56.48; H, 6.09; N, 20.80%

Example 76

0.8 mmol) in aqueous sodium hydroxide (0.26 M, 1 mL) and the resultant solution heated to 30°C for 16 h. Ethanol was removed *in vacuo* and water (10 mL) added and the resulting solution acidified to pH 2 (conc. hydrochloric acid) prior to extraction with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated and the residue purified by column chromatography (eluting with a gradient of ethyl acetate:pentane (20:80 to 100:0) and then ethyl acetate: methanol (90:10)) **[OK?]** and the desired product crystallised from methanol to give the title compound as a white solid (35 mg, 0.1 mmol).

m.p. 239-241°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (t, 3H), 1.85-2.1 (m, 4H), 2.95 (t, 2H), 4.25 (s, 3H), 4.6 (t, 2H), 6.35 (s, 1H), 8.65 (s, 1H), 9.05 (s, 1H), 11.05 (s, 1H).

LRMS (TSP) 411 (MH^+).

Analysis: found C, 58.41; H, 5.41; N, 20.31. Calcd for $C_{22}H_{22}N_6O_4$: C, 58.53; H, 5.40; N, 20.48%

Example 74

5-(5-Amino-2-propoxy-3-pyridinyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one and

Example 74a

Benzyl 5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxy-3-pyridinylcarbamate

The title compound of Preparation 36 (3.0 g, 6.1 mmol) and potassium hexamethyldisilazide (1.97 g, 12.2 mmol) in *tert*-butanol (200 mL) were heated to 80°C for 2 h, allowed to cool, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (150 mL) and washed with water (75 mL) and brine (50 mL), dried over $MgSO_4$, and purified by column chromatography (eluting with a gradient of ethyl acetate:pentane (20:80 to 50:50)). Two components were isolated. The more lipophilic (R_f=0.75 in

pyrimidin-5-yl)-6-propoxy-3-pyridinyl]-2-propynoate

A solution of ethyl propiolate (0.2 mL, 1.9 mmol) in tetrahydrofuran (5 mL) was cooled to –65°C and sec-butyllithium (1.3 M in cyclohexane, 1.5 mL, 1.9 mmol) added maintaining temperature <-65°C. After 1 h, a solution of zinc chloride in tetrahydrofuran (0.5 M, 12 mL, 5.7 mmol) was added and the mixture allowed to warm to room temperature, stirred for a further 0.5 h, cooled in ice and the product of Example 69 (430 mg, 0.95 mmol) added in tetrahydrofuran (5mL) together with dichlorobis(triphenylphosphine)palladium(II) (35 mg) in tetrahydrofuran (2 mL). The reaction mixture was heated to 50°C for 2 h, additional dichlorobis (triphenylphosphine)palladium(II) (35 mg) added and the mixture heated for a further 3 h. After cooling, water (5 mL) and diethyl ether (5 mL) were added, the mixture filtered through Celite®, and the aqueous phase extracted with diethyl ether (3 x 15 mL). Combined organics were washed with brine (15 mL), dried over $MgSO_4$, concentrated to a residue and purified by column chromatography (ethyl acetate:pentane (1:4) as eluant). The title compound was formed as a pale yellow solid (128 mg, 0.3 mmol) after crystallisation from diisopropylether.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (t, 3H), 1.4 (t, 3H), 1.8-2.1 (m, 4H), 2.9 (t, 2H), 4.25 (s, 3H), 4.35 (t, 2H), 4.6 (t, 2H), 8.5 (s, 1H), 8.95 (s, 1H), 10.9 (s, 1H).

LRMS (TSP) 424 (MH^+).

Analysis: found C, 61.84; H, 5.89; N, 16.33. Calcd for $C_{22}H_{25}N_5O_4.0.25H_2O$: C, 61.74; H, 6.01; N, 16.36%

Example 73

5-[5-(3-Hydroxy-5-isoxazolyl)-2-propoxy-3-pyridinyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

A suspension of the title compound of Example 72 (110 mg, 0.3 mmol) in ethanol (10 mL) was added to hydroxylamine hydrochloride (54 mg,

(dichloromethane : methanol (99:1) as eluant) to give the title compound as a white solid (0.83 g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (t, 3H), 1.8-2.05 (m, 4H), 2.95 (t, 2H), 4.25 (s, 3H), 4.55 (t, 2H), 8.45 (s, 1H), 9.05 (s, 1H), 10.9 (s, 1H).

LRMS (ES – negative ion) 452 (M-H), (ES – positive ion) 454 (MH^+).

Analysis: found C, 44.92; H, 4.36; N, 15.33. Calcd for $C_{17}H_{20}IN_5O_2$: C, 45.05; H, 4.45; N, 15.45%

Example 70

5-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-6-propoxynicotinonitrile

The title compound was prepared from the title compound of Example 69 using the method of Example 35.

m.p. 174-6°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.2 (t, 3H), 1.8-2.1 (m, 4H), 2.95 (t, 2H), 4.25 (s, 3H), 4.65 (t, 2H), 8.55 (s, 1H), 9.1 (s, 1H), 10.8 (s, 1H).

LRMS (TSP) 353 (MH^+).

Example 71

1-Methyl-5-[2-propoxy-5-(1*H*-tetrazol-5-yl)-3-pyridinyl]-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared from the product of Example 70 using the method of Example 43.

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.9-1.05 (m, 6H), 1.65-1.85 (m, 4H), 2.8 (t, 2H), 4.15 (s, 3H), 4.4 (t, 2H), 8.55 (s, 1H), 8.95 (s, 1H), 12.2 (s, 1H).

LRMS (TSP) 396 (MH^+).

Example 72

Ethyl 3-[5-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]-

Example 68

[5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetic acid

The product of Example 64 (100 mg, 0.19 mmol) was dissolved in acetonitrile (3 mL) at 30°C and tri-orthotolylphosphine (10 mg, 0.03 mmol), palladium acetate (3.5 mg), triethylamine (44 µL, 0.32 mmol) and butyl vinyl ether (51 µL, 0.39 mmol) were added. The resultant mixture was heated to reflux for 10 h, allowed to cool to room temperature, hydrochloric acid (6 M, 1.5 mL) was added and the mixture allowed to stir at room temperature for 6 h. Water (5 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 5 mL). Combined organic extracts were washed with saturated brine (5 mL), dried over Na_2SO_4, and concentrated to a yellow gum. Purification by column chromatography (dichloromethane : methanol : acetic acid (90:10:1) as eluant) gave a residue which was crystallised from ethyl acetate and further purified by column chromatography (dichloromethane : methanol : acetic acid (90:10:1) as eluant) and finally crystallised from ethyl acetate to afford a white solid (18 mg, 0.04 mmol).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.95 (t, 3H), 1.3 (t, 3H), 1.7-1.85 (m, 2H), 2.6 (s, 3H), 2.85 (q, 2H), 4.4 (t, 2H), 5.25 (s, 2H), 8.05 (s, 1H), 8.95 (s, 1H), 12.3 (br s, 1H).

LRMS (ES – negative ion) 354 (M-CO_2H), 398 (M-H).

Example 69

5-(2-Propoxy-5-iodo-3-pyridinyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from Preparation 33 (1.0 g, 2.1 mmol) was dissolved in propanol (25 mL), potassium *tert*-butoxide (200 mg, 1.8 mmol) added, and the resultant mixture heated to reflux for 3.5 h. After removal of the propanol *in vacuo*, the residue was purified by column chromatography

Example 67

[3-Ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]acetic acid

The title compound was prepared in 65% yield from *tert*-butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-2-yl]acetate (the compound of Example 65) using the method of Example 66 to yield a while solid.

^{1}H NMR (400 MHz, F_3CCO_2D): δ = 0.95 (t, 3H), 1.3 (t, 3H), 1.8-1.95 (m, 2H), 3.05 (q, 2H), 4.5 (t, 2H), 5.4 (s, 2H), 8.5 (s, 1H), 8.85 (s, 1H).

LRMS (ES – positive ion) 484 (MH^+), 506 (MNa^+). (ES – negative ion) 438 ($M-CO_2H$), 482 (M-H).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1 (t, 3H), 1.4 (t, 3H), 1.5(s, 9H), 1.9-2.05 (m, 2H), 3.05 (q, 2H), 4.5 (t, 2H), 5.25 (s, 2H), 8.45 (s, 1H), 9.05 (s, 1H), 11.0 (br s, 1H).

LRMS (TSP) 541 (MH^+).

Analysis: found C, 46.76; H, 4.83; N, 12.85. Calcd for $C_{21}H_{26}IN_5O_4$: C, 46.75; H, 4.86; N, 12.98%

The second isomer (the compound of Example 65) - *tert*-butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-2-yl]acetate was also crystallised from diisopropyl ether (147 mg, 0.27 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.4-1.6 (m, 12H), 1.95-2.05 (m, 2H), 3.0 (q, 2H), 4.6 (t, 2H), 5.0 (s, 2H), 8.4 (s, 1H), 8.95 (s, 1H), 10.75 (br s, 1H).

LRMS (TSP) 541 (MH^+), 558 (MNH_4^+).

Analysis: found C, 46.71; H, 4.83; N, 12.86. Calcd for $C_{21}H_{26}N_5O_4I$: C, 46.75; H, 4.86; N, 12.98%

The isomers were distinguished by nOe studies.

Example 66

[3-Ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetic acid

The title compound of Example 64 (50 mg, 0.1 mmol) was dissolved in trifluoroacetic acid (0.5 mL) and the solution stood at room temperature overnight. The trifluoroacetic acid was removed by evaporation and the resultant gum taken up in ethyl acetate (2 mL). A white solid crystallised out and was washed with further ethyl acetate to give the title compound (63% yield).

^{1}H NMR (400 MHz, F_3CCO_2D): δ = 0.95 (t, 3H), 1.3 (t, 3H), 1.8-1.95 (m, 2H), 3.0 (q, 2H), 4.55 (t, 2H), 5.6 (s, 2H), 8.55 (s, 1H), 8.9 (s, 1H).

LRMS (ES – positive ion) 484 (MH^+), 506 (MNa^+). (ES – negative ion) 438 ($M-CO_2H$), 482 (M-H).

acetate and water whereupon a white solid precipitated which was separated by filtration. The organic phase was separated, dried over Na_2SO_4, concentrated and combined with the above solid, and this then washed with ethyl acetate and recrystallised from hot methanol-dichloromethane to afford the title compound as a white solid (553 mg, 1.3 mmol).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.9 (t, 3H), 1.3 (t, 3H), 1.6-1.8 (m, 2H), 2.8-2.95 (2H, br m), 4.25 (t, 2H), 8.25 (s, 1H), 8.5 (s, 1H).

LRMS (TSP) 426 (MH^+), 443 (MNH_4^+).

Analysis: found C, 42.40; H, 3.69; N, 16.39. Calcd for $C_{15}H_{16}IN_5O_2$: C, 42.37; H, 3.796; N, 16.47%

Examples 64 and 65

tert-Butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetate and *tert*-butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]acetate

A solution of title compound of Example 63 (450 mg, 1.1 mmol) in *N,N*-dimethylformamide (10 mL) was treated with cesium carbonate (345 mg, 1.1 mmol) and *tert*-butyl bromoacetate (156 µL, 1.1 mmol). After stirring at room temperature for 2 h, additional *tert*-butyl bromoacetate (50 µL, 0.3 mmol) was added and the reaction stirred for a further 0.5 h. The reaction mixture was diluted with water (75 mL) and extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4 and concentrated, and the residue purified by flash column chromatography (dichloromethane : methanol : 0.88 ammonia (95:5:0.5) as eluant). The first isomer to be eluted off the column was the compound of Example 64 - *tert*-butyl [3-ethyl-5-(5-iodo-2-propoxy-3-pyridinyl)-7-oxo-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-1-yl]acetate, which was crystallised from diisopropyl ether (83 mg, 0.15 mmol).

LRMS (TSP): 407.3 (MH^+).

Example 62

N-[6-Ethoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)-3-pyridinyl]nicotinamide

Nicotinic acid (68 mg, 0.55 mmol) in dichloromethane (2 mL) was treated with oxalyl chloride (0.24 mL, 2.75 mmol) under a nitrogen atmosphere and 1 drop of *N*,*N*-dimethylformamide was added. After 2 h solvent was removed *in vacuo* azeotroping twice with dichloromethane to give a white solid. To this solid was added 5-(5-amino-2-ethoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 60) (150 mg, 0.46 mmol), dichloromethane (5 mL) and triethylamine (0.16 mL, 1.15 mmol) and the reaction mixture was stirred for 2 h. The mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate (twice). The combined organics were dried ($MgSO_4$) and concentrated to give a beige semi-solid. Flash column chromatography (gradient elution from 5% methanol:dichloromethane to 10% methanol:dichloromethane) gave 35 mg of the product as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H), 1.45 (t, 3H), 1.80 (m, 2H), 2.90 (t, 2H), 4.00 (s, 3H), 4.60 (q, 2H), 7.40 (m, 1H), 8.25 (d, 1H), 8.65 (m, 2H), 9.00 (s, 1H), 9.20 (s, 1H), 10.00 (s, 1H), 10.90 (s, 1H).

TLC (10% methanol:dichloromethane) - R_f = 0.42

Example 63

5-(2-Propoxy-5-iodo-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl]nicotinate

A solution of the title compound from Preparation 32 (1.0 g, 2.3 mmol) in *n*-propanol (10 mL) and ethyl acetate (0.5 mL) was treated with potassium *tert*-butoxide (253 mg, 2.3 mmol) and heated to reflux for 24 h. After evaporation to dryness, the reaction mixture was partitioned between ethyl

Example 60

5-(5-Amino-2-ethoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Potassium t-butoxide (15.5 g, 0.14 mol) was added to a stirred solution of the title compound from Preparation 23 (12 g, 35 mmol) in *t*-butanol (300 mL). The mixture was refluxed for 39 h and then cooled (reaction had not gone to completion). The solvent was removed in vacuo and the resulting thick mixture dissolved in water and neutralised to pH 5 with 2 *N* hydrochloric acid. The aqueous was extracted with dichloromethane (3 times) and the organics were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (ethyl acetate as eluant) gave 1.5 g of desired product and recovered starting material.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.50 (t, 3H), 1.80 (m, 2H), 3.00 (t, 2H), 3.60 (br s, 2H), 4.10 (s, 3H), 4.60 (q, 2H), 7.80 (s, 1H), 8.20 (s, 1H), 11.15 (s, 1H).

Example 61

N-[6-Ethoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinyl]methanesulfonamide

Methanesulfonyl chloride (0.056 mL, 7.24 mmol) was added to a stirred solution of 5-(5-amino-2-ethoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 60) (158 mg, 0.48 mmol) in pyridine (3 mL) at room temperature for 16 h. The mixture was partitioned between 3% sodium bicarbonate solution and ethyl acetate. The organic layer was washed with 0.5 *N* hydrochloric acid and water, dried ($MgSO_4$) and evaporated to give 0.1 g of a yellow solid. Trituration with dichloromethane (twice) gave the product as a yellow solid (50 mg).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.95 (t, 3H), 1.30 (t, 3H), 1.70 (m, 2H), 2.90 (t, 2H), 3.00 (s, 3H), 4.00 (s, 3H), 4.40 (q, 2H), 7.95 (s, 1H), 8.15 (s, 1H), 9.65 (br s, 1H), 11.60 (s, 1H).

Example 59

5-(5-Acetyl-2-ethoxy-3-pyridinyl)-3-[6-(dimethylamino)-3-pyridinyl]-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Potassium carbonate (35 mg, 0.25 mmol), 6-(dimethylamino)pyridin-3-yl boronic acid dihydrochloride (42 mg, 0.25 mmol) and 5-(5-acetyl-2-ethoxy-3-pyridinyl)-3-bromo-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one (Example 58) (50 mg, 0.13 mmol) were suspended in dioxan/water (2 mL of a 4:1 mix) and the reaction mixture was immersed in a pre-heated oil bath (120°C) for 5 min. The mixture was cooled and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) was added. The mixture was reheated to reflux for 2 h. More $Pd(PPh_3)_4$ (15 mg, 0.012 mmol) and 6-(dimethyl-amino)pyridin-3-yl boronic acid dihydrochloride (32 mg, 0.25 mmol) were added and reflux was continued for 14 h. The cooled reaction mixture was concentrated and the residue partitioned between dichloromethane and water and filtered through a plug of Celite®. The organic layer was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), filtered and evaporated. The yellow residual solid was purified by flash column chromatography (gradient elution from dichloromethane/0.2% ammonia to 99% dichloromethane/methanol/0.5% ammonia) to give 30 mg of the title compound. Further purification by trituration with ether and recrystallisation from isopropyl alcohol to give 18 mg of pure product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (t, 3H), 2.60 (s, 3H), 3.20 (s, 6H), 4.20 (s, 3H), 4.80 (q, 2H), 6.70 (d, 1H), 7.80 (d, 1H), 8.40 (s, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.75 (s, 1H).

LRMS (TSP) 434.5 (MH^+).

5-(5-Acetyl-2-ethoxy-3-pyridinyl)-3-bromo-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

A mixture of 3-bromo-5-(2-ethoxy-5-ethynyl-3-pyridinyl)-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 57) (750 mg, 2 mmol), 1N H_2SO_4 (2 mL) and $HgSO_4$ (50 mg, 0.17 mmol) in acetone (25 mL) was stirred at reflux for 10 h then at room temperature for 14 h. Further H_2SO_4 (5 mL of 1N) was added and refluxing was continued for a further 4 h. The mixture was cooled and the solvent evaporated and the residue partitioned between dichloromethane and water. After basifying with solid sodium bicarbonate a white precipitate formed which was filtered off before separating the phases. The organic layer was dried ($MgSO_4$), concentrated and combined with the solid previously filtered to give the title compound as a poorly soluble solid.

^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.30 (t, 3H), 2.60 (s, 3H), 4.10 (s, 3H), 4.40 (q, 2H), 8.40 (s, 1H), 8.90 (s, 1H), 12.00 (br s, 1H).

LRMS (TSP): 393.7 (MH^+).

3-Bromo-5-(2-ethoxy-5-iodo-3-pyridinyl)-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Butyl nitrite (282 mg, 2.74 mmol) was added dropwise to a stirred suspension of the title compound of Example 54 (200 mg, 0.55 mmol) in diiodomethane (2 mL) at room temperature. After 1 h the reaction was warmed for 2 h at 40-50°C. The mixture was cooled and purified directly by flash column chromatography (gradient elution from dichloromethane to 98% dichloromethane/5% methanol) to give the product as a brown solid (60 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (t, 3H), 4.15 (s, 3H), 4.60 (q, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.90 (s, 1H).

LRMS (TSP): 475.6 (MH^+).

Example 56 (Preparative example)

3-Bromo-5-(2-ethoxy-5-trimethylsilylethynyl-3-pyridinyl)-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 14 using the title compound of Example 55.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.55 (t, 3H), 4.20 (s, 3H), 4.65 (q, 2H), 8.40 (s, 1H), 8.85 (s, 1H), 10.95 (s, 1H).

LRMS (TSP): 446.3 and 448.5 (MH^+).

Example 57

3-Bromo-5-(2-ethoxy-5-ethynyl-3-pyridinyl)-2-methyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 15 using the title compound of Example 56.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (t, 3H), 3.20 (s, 1H), 4.10 (s, 3H), 4.65 (q, 2H), 8.35 (s, 1H), 8.80 (s, 1H), 10.90 (s, 1H).

LRMS (ES): 373 (MH^+).

Example 58

The filtrate was separated, and the organic layer washed with aqueous saturated sodium bicarbonate solution, and brine, then dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow solid. The isolated solids were combined, suspended in ethyl acetate, and stirred for 30 minutes. The resulting precipitate was filtered off, and dried to afford the title compound (7.66 g, 89%).

^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.35 (t, 3H), 4.10 (s, 3H), 4.54 (q, 2H), 8.70 (d, 1H), 9.20 (d, 1H), 12.16 (s, 1H).

LRMS 394.6 $(MH)^+$

Found: C, 39.51: H, 2.80; N, 21.27. $C_{13}H_{11}BrN_6O_4$ requires C, 39.63; H, 2.73; N, 21.36%.

Example 54

3-Bromo-5-(5-amino-2-ethoxy-pyridin-3-yl)-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one

Titanium trichloride (20.93 g, 140 mL of a 15% solution in hydrochloric acid) was added to a solution of 3-bromo-5-(2-ethoxy-5-nitropyridin-3-yl)-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 53) (7.66 g, 19.4 mmol) in acetic acid (100 mL). After 2 h the acetic acid was evaporated and azeotroped with toluene. The residue was partitioned between sodium bicarbonate solution and dichloromethane and the titanium salts filtered to aid separation of the aqueous and organic phases. The aqueous layer was saturated with sodium chloride and re-extracted with dichloromethane. The organics were dried ($MgSO_4$) and concentrated to give a solid. Trituration with ethyl acetate gave 3 g of pure product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3H), 3.80 (br s, 2H), 4.00 (s, 3H), 4.40 (q, 2H), 7.65 (s, 1H), 8.10 (s, 1H), 11.15 (s, 1H).

LRMS (TSP): 363.8, 366.8 (MH^+).

Example 55

Example 52

5-(2-Ethoxy-5-nitropyridin-3-yl)-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one

A mixture of the title compounds of Preparations 29 (3.85 g, 27.5 mmol) and 26 (8.26 g, 30.6 mmol) in 3-methyl-3-pentanol (80 mL) was heated under reflux for 2½ h, then cooled. The reaction mixture was partitioned between dichloromethane and hydrochloric acid (2N), and the resulting precipitate filtered, washed with water and diethyl ether, and dried. The filtrate was separated, and the organic layer washed with hydrochloric acid (2N), saturated aqueous sodium bicarbonate solution, brine, then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was triturated with diethyl ether, and the resulting solid filtered and dried. The isolated solids were combined to provide the title compound (6.9 g, 79%).

^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.35 (t, 3H), 4.10 (s, 3H), 4.54 (q, 2H), 8.39 (s, 1H), 8.70 (d, 1H), 9.19 (d, 1H), 11.92 (s, 1H).

LRMS 317 $(MH)^+$

Found: C, 49.36; H, 3.82; N, 26.57. $C_{13}H_{12}N_6O_4$ requires C, 49.18; H, 3.77; N, 26.53%.

Example 53

3-Bromo-5-(2-ethoxy-5-nitropyridin-3-yl)-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one

A mixture of the title compound of Example 52 (6.9 g, 21.8 mmol), bromine (1.35 mL, 26.2 mmol), and sodium acetate (2.7 g, 32.7 mmol) in acetic acid (100 mL) was heated under reflux for 7 h, then allowed to cool. Additional bromine (0.35 mL, 6.8 mmol) was added and the reaction stirred at room temperature for a further 18 h. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was partitioned between dichloromethane and water and the resulting precipitate filtered off, washed with dichloromethane, water, then diethyl ether and dried.

continued for 14 h. Further formaldehyde (0.01 mL of 37-41% solution) and sodium triacetoxyborohydride (108 mg, 0.51 mmol) were added and stirring continued for a further 4.5 h. Starting material still remained so further formaldehyde (0.01 mL of 37-41% solution) and sodium triacetoxyborohydride (108 mg, 0.51 mmol) were added and stirring continued for a further 18 h. The reaction mixture was diluted with dichloromethane, washed with sodium bicarbonate solution then brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (elution with 94:6:0.6 dichloromethane/methanol/0.88 ammonia) gave the product (41 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 4H), 2.15 (t, 2H), 2.35 (s, 3H), 2.55 (m, 2H), 2.65 (s, 3H), 3.00 (m, 4H), 4.20 (m, 1H), 4.65 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.50 (s, 1H).

LRMS (TSP): 453.4 (MH^+).

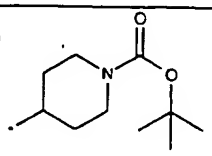
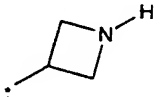
Example 51a

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 51 using Example 50a as starting material.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.95 (m, 2H), 2.50 (s, 3H), 2.60 (s, 3H), 3.00 (q, 2H), 3.80 (t, 2H), 3.90 (t, 2H), 4.65 (t, 2H), 5.10 (m, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.65 (s, 1H).

LRMS (TSP): 425.6 (MH^+).

			(t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (br s, 1H).
50*		539.5	(300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.45 (s, 9H), 1.50 (m, 2H), 1.90 (m, 4H), 2.40 (m, 2H), 2.65 (s, 3H), 2.90 (m, 2H), 3.10 (q, 2H), 4.30 (br s, 3H), 4.65 (m, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).
50a**		411.6	(300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.35 (t, 3H), 1.50 (m, 2H), 1.95 (m, 2H), 2.60 (s, 3H), 3.00 (q, 2H), 3.90 (t, 2H), 4.55 (t, 2H), 4.70 (t, 2H), 5.40 (m, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.65 (br s, 1H).

*The acid mediated hydrolysis of the acetylene to the acetyl (as in Example 47) resulted in the formation of both the title compounds of Example 49 and Example 50 through hydrolysis of the *tert*-butylcarbamate functionality under the reaction conditions.

** The acid mediated hydrolysis of the acetylene to the acetyl (as in Example 47) was left for an extended period of time to facilitate complete hydrolysis of the *tert*-butylcarbamate functionality under the reaction conditions.

Example 51

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-methyl-4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(4-piperidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 49) (100 mg, 0.23 mmol) was dissolved in dichloromethane (10 mL) and formaldehyde (27 mg, 0.01 mL of a 37-41% solution) was added. After 30 min stirring sodium triacetoxyborohydride (108 mg, 0.51 mmol) was added and stirring

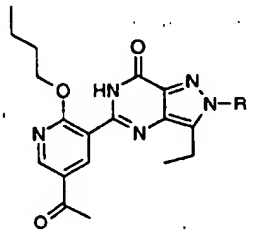
the residue partitioned between ethyl acetate (100 mL) and saturated sodium bicarbonate solution (100 mL). The aqueous was washed with a further 100 mL of ethyl acetate and the combined organics dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (elution with 95% dichloromethane/methanol) gave the product as a cream coloured solid (140 mg)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.60 (s, 3H), 2.90 (t, 2H), 3.05 (q, 2H), 4.40 (t, 2H), 4.70 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).

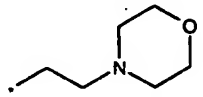
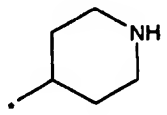
LRMS (TSP): 427.5 (MH^+).

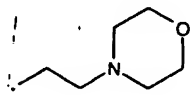
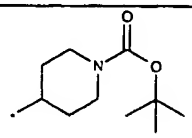
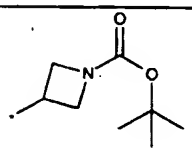
Examples 47a to 47c

The following compounds were made by the method of Example 47



from the appropriate acetylene compounds.

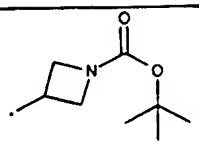
Ex.	R	LRMS $(MH)^+$	^{1}H NMR
48		469	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.50 (m, 4H), 2.65 (s, 3H), 2.95 (t, 2H), 3.10 (q, 2H), 3.65 (m, 4H), 4.40 (t, 2H), 4.65 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).
49*		440	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 4H), 1.90 (m, 4H), 2.35 (m, 2H), 2.60 (s, 3H), 2.80 (t, 2H), 3.10 (q, 2H), 3.30 (d, 2H), 4.40 (m, 1H), 4.45

Ex.	R	LRMS $(MH)^+$	^1H NMR
46a		451	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.50 (m, 4H), 2.95 (t, 2H), 3.05 (q, 2H), 3.20 (s, 1H), 3.70 (m, 4H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.75 (s, 1H).
46b		521	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.50 (s, 9H), 1.90 (m, 4H), 2.40 (br s, 2H), 2.90 (br s, 2H), 3.05 (q, 2H), 3.20 (s, 1H), 4.40 (m, 3H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).
46c		393.3	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.35 (t, 3H), 1.50 (s, 9H), 1.55 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 3.20 (s, 1H), 4.35 (t, 2H), 4.60 (t, 2H), 4.65 (br s, 2H), 5.20 (m, 1H), 8.40 (s, 1H), 8.80 (s, 1H), 10.80 (s, 1H).

Example 47

5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

1 *N* Sulfuric acid (1 mL) was added to a stirred solution of 5-(2-butoxy-5-ethynyl-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 46) (280 mg, 0.69 mmol) in acetone (8 mL) at room temperature. Mercury sulfate (40 mg, 0.14 mmol) was added and the mixture heated at reflux for 5 h. The reaction mixture was cooled, diluted with methanol (10 mL) , filtered and the filtrate washed with further methanol. The solvent was evaporated and

45c		582.4 - MH^+	(400 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.40 (s, 9H), 1.50 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 4.40 (t, 2H), 4.50 (t, 2H), 4.60 (br s, 2H), 5.25 (m, 1H), 8.40 (s, 1H), 8.80 (s, 1H), 10.80 (s, 1H).

Example 46

5-(2-Butoxy-5-ethynyl-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

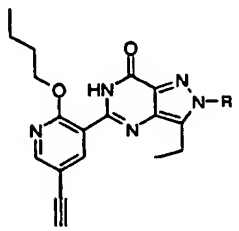
Potassium fluoride (72.5 mg, 1.25 mmol) was added to a stirred solution of 5-(2-butoxy-5-trimethylsilylethynyl-3-pyridinyl)-2-[2-(dimethylamino)-ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 45) (300 mg, 0.625 mmol) in *N*,*N*-dimethylformamide (10 mL) and water (2 mL) at room temperature. After 2 h the reaction mixture was poured into brine and extracted with ethyl acetate (2 x 100 mL) The organics were dried ($MgSO_4$) and concentrated to give the product (285 mg) as a pale brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.30 (s, 6H), 2.90 (t, 2H), 3.00 (q, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).

LRMS (ES): 409 (MH^+).

Examples 46a to 46c

The following compounds were made by the method of Example 46



from the appropriate trimethylsilyl compounds.

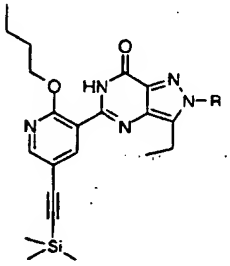
were dried ($MgSO_4$) and concentrated to give a yellow solid. Purification by flash column chromatography (elution with 5% methanol/ 95% dichloromethane) gave the product as a pale brown oil (290 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.30 (s, 3H), 2.90 (t, 2H), 3.05 (q, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.30 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).

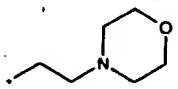
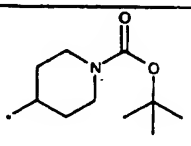
LRMS (TSP): 481.3 (MH^+).

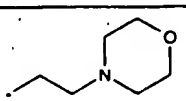
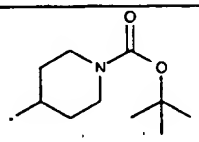
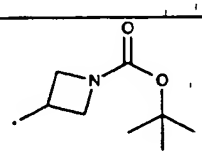
Examples 45a to 45c

The following compounds were made by the method of Example 45:



from the appropriate iodo compounds.

Ex.	R	LRMS	^{1}H NMR
45a		523 MH^+	(300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.50 (m, 4H), 2.95 (t, 2H), 3.05 (q, 2H), 3.70 (m, 4H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).
45b		615 -MNa^+	(400 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (s, 9H), 1.55 (m, 2H), 1,90 (m, 4H), 2.40 (br s, 2H), 2.85 (br s, 2H), 3.10 (m, 2H), 4.40 (m, 3H), 4.60 (t, 2H), 8.35 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).

Ex.	R	LRMS $(MH)^+$	^1H NMR
44a		553	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 2.50 (m, 4H), 2.95 (t, 2H), 3.05 (q, 2H), 3.65 (m, 4H), 4.40 (t, 2H), 4.50 (t, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.70 (s, 1H).
44b		623	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (s, 9H), 1.55 (m, 2H), 1.90 (m, 4H), 2.40 (br s, 2H), 2.90 (br s, 2H), 3.10 (q, 2H), 4.30 (m, 3H), 4.60 (t, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.70 (s, 1H).
44c		612.2	(400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (s, 9H), 1.55 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 4.40 (t, 2H), 4.50 (t, 2H), 4.65 (br s, 2H), 5.20 (m, 1H), 8.40 (s, 1H), 9.00 (s, 1H), 10.80 (s, 1H).

Example 45 (Preparative example)

5-(2-Butoxy-5-trimethylsilylethynyl-3-pyridinyl)-2-[2-(dimethylamino)-ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

$Pd(PPh_3)_2Cl_2$ (11.2 mg, 0.016 mmol) and cuprous iodide (3 mg, 0.016 mmol) were added to a stirred slurry of 5-(2-butoxy-5-iodo-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one (Example 44) (330 mg, 0.647 mmol) in triethylamine (8 mL) and acetonitrile (2 mL) at room temperature under a nitrogen atmosphere. The mixture was heated at 60°C for 3 h, cooled and extracted from brine with dichloromethane (2 x 100 mL). The organics

mixture was transferred to a PTFE lined sealed vessel, a further 0.069 mL trimethylsilylazide added and the reaction heated at 80°C for a further 5 h. After cooling and filtering the filtrate was diluted with pentane. Further solid precipitated and this was combined with the original precipitate and purified by flash column chromatography (eluting with dichloromethane/methanol/ammonia in a ratio of 5:1:0.1) to give 144 mg product.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.20 (m, 1H), 3.10 (t, 2H), 4.10 (s, 3H), 4.35 (d, 2H), 8.90 (s, 1H), 8.95 (s, 1H).

LRMS (ES): 410.1 (MH^+).

Example 44

5-(2-Butoxy-5-iodo-3-pyridinyl)-2-[2-(dimethylamino)ethyl]-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

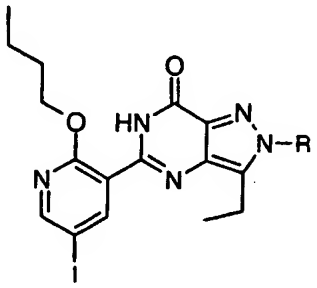
The title compound was made by the method of Example 1, from Preparation 17.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.85 (m, 2H), 2.30 (s, 3H), 2.80 (t, 2H), 3.00 (q, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.95 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 511.3 (MH^+).

Examples 44a to 44c

The following compounds were made by the method of Example 44



from the appropriate pyrazolocarboxamides.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 2.70 (s, 3H), 3.00 (t, 2H), 4.05 (s, 3H), 4.40 (d, 2H), 8.95 (s, 1H), 9.35 (s, 1H), 10.70 (s, 1H).

LRMS (ES): 424.1 (MH^+).

Example 42

5-[2-Isobutoxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Iodo-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 22) (200 mg, 0.42 mmol) and *N*-hydroxyethanimidamide (EP 795 328) (95 mg, 1.28 mmol) were suspended in toluene (4 mL) and triethylamine (86 mg, 0.85 mmol) was added. $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol) was added and placed in a pre-heated oil bath at 95°C under 1 atmosphere carbon monoxide. After 4 h a further portion of acetamidoxime (50 mg), triethylamine (43 mg) and $Pd(PPh_3)_2Cl_2$ (15 mg) were added and stirring was continued at 95°C for 14 h. The cooled reaction mixture was diluted with ethyl acetate and washed with water and brine, dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (gradient elution from dichloromethane : 1% methanol:dichloromethane) gave 70 mg product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 2.50 (s, 3H), 3.00 (t, 2H), 4.10 (s, 3H), 4.45 (d, 2H), 9.00 (s, 1H), 9.40 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 424.1 (MH^+).

Example 43

5-[2-Isobutoxy-5-(1*H*-1,2,3,4-tetrazol-5-yl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-[2-Isobutoxy-5-cyano-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 36) (200 mg, 0.55 mmol), trimethylsilylazide (0.069 mL, 0.54 mmol) and dibutyltin oxide (54 mg, 0.22 mmol) were heated at 80°C in toluene (10 mL) for 14 h. The reaction

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, 3H), 0.95 (d, 6H), 1.60 (m, 2H), 2.10 (m, 1H), 2.80 (t, 2H), 3.90 (s, 3H), 4.20 (d, 2H) 5.00 (br s, 2H), 8.40 (s, 1H), 8.70 (s, 1H), 9.35 (s, 1H)., 10.70 (s, 1H).

LRMS (TSP): 399.8 MH^+).

Example 40 (Preparative example)

5-{5-[[(Acetyloxy)imino](amino)methyl]-2-isobutoxy-3-pyridinyl}-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

N-Hydroxy-6-isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinecarboximidamide (Example 39) (65 mg, 0.16 mmol), *N*,*N*-dimethylaminopyridine (24 mg, 0.20 mmol), acetic acid (9.7 mg, 0.16 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (37.5 mg, 0.20 mmol) were stirred in dioxan (2 mL) for 14 h. The solvent was removed *in vacuo* and the product purified by flash column chromatography (eluting with 90% dichloromethane:methanol) to give the product (58 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (s, 3H), 2.25 (m, 1H), 2.95 (t, 2H), 4.00 (s, 3H), 4.40 (d, 2H), 5.25 (br s, 2H), 8.60 (s, 1H), 8.75 (s, 1H), 10.70 (s, 1H).

LRMS (EI): 442.1 (MH^+).

Example 41

5-[2-Isobutoxy-5-(5-methyl-1,2,4-oxadiazol-3-yl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-{5-[[(Acetyloxy)imino](amino)methyl]-2-isobutoxy-3-pyridinyl}-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 40) (55 mg, 0.13 mmol) was heated at 190°C for 3 h. After cooling the oxadiazole was purified by flash column chromatography (elution with 50:1 dichloromethane:methanol) to give 21 mg of a yellow solid.

Example 38

5-[2-isoButoxy-5-(4-methyl-1,3-thiazol-2-yl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

6-Isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)-3-pyridinecarbothioamide (Example 37) (77 mg, 0.19 mmol) and chloroacetone (36 mg, 0.38 mmol) were heated to reflux for 14 h in ethanol (5 mL). The reaction mixture was cooled and concentrated. Purification by flash column chromatography (gradient elution from 100% dichloromethane to 3% methanol:dichloromethane) gave 65 mg of product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.85 (m, 2H), 2.30 (m, 1H), 2,55 (s, 3H), 3.00 (t, 2H), 4.10 (s, 3H), 4.40 (d, 2H), 6.90 (s, 1H), 8.80 (s, 1H), 9.20 (s, 1H), 10.75 (s, 1H).

LRMS (TSP): 438.9 (MH^+).

Example 39 (Preparative example)

N-Hydroxy-6-isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinecarboximidamide

Potassium t-butoxide (61 mg, 0.54 mmol) was added to a stirred suspension of hydroxylamine hydrochloride (38 mg, 0.54 mmol) in 2-methyl-1-propanol (5 mL). After 2-3 min 6-isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)nicotinonitrile (Example 36) (200 mg, 0.54 mmol) was added and the reaction mixture heated at reflux for 5 h. A further 1 equivalent of potassium *t*-butoxide and hydroxylamine hydrochloride were added and refluxing continued for 14 h. The reaction mixture was cooled and concentrated. The residue was triturated with dichloromethane and filtered, washing the solid with further dichloromethane. The filtrate was evaporated and purified by flash column chromatography (elution with ethyl acetate + 2% ammonia) gave 65 mg of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 3.00 (t, 2H), 4.10 (s, 3H), 4.40 (d, 2H), 8.60 (s, 1H), 9.00 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 367.0 (MH^+).

Example 37 (Preparative example)

6-Isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-3-pyridinecarbothioamide

Water (2 drops) was added to a stirred suspension of 6-isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-nicotinonitrile (Example 36) (150 mg, 0.41 mmol) in $(EtO)_2P(S)SH$ (0.5 mL). The mixture was stirred at room temperature. After 5 h more $(EtO)_2P(S)SH$ (0.5 mL) was added and dichloromethane (5 mL) added to aid stirring. After 14 h the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. After filtration and separation of the phases the organics were washed again with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$) and concentrated. The product was purified by flash column chromatography (gradient elution from 100% dichloromethane to 96% dichloromethane : methanol) to give 80 mg product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3H), 0.95 (d, 6H), 1.70 (m, 2H), 2.10 (m, 1H), 2.80 (t, 2H), 3.90 (s, 3H), 4.20 (d, 2H), 8.60 (br s, 1H), 8.70 (s, 1H), 8.75 (br s, 1H), 9.00 (s, 1H), 10.65 (s, 1H).

LRMS (TSP): 366.9 (MH^+).

(54 mg, 0.62 mmol) and triethylamine (84 mg, 0.83 mmol) were added and the mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated and the residue dissolved in ethyl acetate, washed with water (twice), saturated sodium bicarbonate (twice) and brine, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (gradient elution 20% ethyl acetate/pentane : 100% ethyl acetate : 3% methanol/ethyl acetate) gave 70 mg product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.95 (m, 2H), 2.60 (m, 4H), 3.05 (q, 2H), 3.25 (s, 3H), 3.75 (m, 6H), 3.90 (t, 2H), 4.45 (t, 2H), 4.65 (t, 2H), 9.00 (s, 1H), 9.40 (s, 1H), 10.60 (s, 1H).

LRMS (ES): 499.1 (MH^+).

Example 35

6-Butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]nicotinonitrile

Copper(I) cyanide (35 mg, 0.39 mmol) was mixed with the title compound of Example 1 (130 mg, 0.26 mmol) in *N*-methylpyrrolidinone (3 mL) and the resulting solution was heated for 14 h at 150°C under a nitrogen atmosphere.. The reaction mixture was cooled and partitioned between ethyl acetate and water. Concentrated ammonium hydroxide was added and the organic layer was separated, washed with more ammonia solution and brine, dried ($MgSO_4$), filtered and evaporated to give a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 3.10 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.65 (t, 2H), 8.55 (s, 1H), 9.00 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 397.2 (MH^+).

Example 36

6-Isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)nicotinonitrile

The title compound was prepared by the method of Example 35.

TLC: R_f = 0.5 (89% dichloromethane:10% methanol:1% ammonia)

Example 33

5-(2-Butoxy-5-glycoloyl-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 29 using Example 15.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.95 (m, 1H), 3.10 (q, 2H), 3.30 (s, 3H), 3.40 (t, 1H), 3.90 (t, 2H), 4.40 (t, 2H), 4.65 (t, 2H), 4.90 (d, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 430.4 (MH^+).

Example 34

5-[2-Butoxy-5-(4-morpholinylacetyl)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one

Triphenylphosphine (110 mg, 0.42 mmol) in dichloromethane (1 mL) was added slowly to an ice cooled solution of 5-(2-butoxy-5-glycoloyl-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one (Example 33) (150 mg, 0.35 mmol) and carbon tetrabromide (140 mg, 0.42 mmol) in dichloromethane (3 mL). The solution was allowed to warm to room temperature. After 2 h further carbon tetrabromide (25 mg, 0.075 mmol) and triphenylphosphine were added and stirring continued for 2 h. Concentration and purification of the product by flash column chromatography (gradient elution with ethyl acetate/pentane (10:90 - 70:30) gave 5-[2-butoxy-5-(2-bromoacetyl)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one which was used without any further purification (slight contamination with triphenylphosphine oxide).

5-[2-Butoxy-5-(2-bromoacetyl)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (205 mg, 0.42 mmol) was dissolved in dichloromethane and the solution cooled to 0°C. Morpholine

column chromatography (eluting with 97% dichloromethane:3% methanol) to give 200 mg of product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.15 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 3.00 (t, 2H), 4.10 (s, 3H), 4.45 (d, 2H), 4.65 (s, 2H), 8.85 (s, 1H), 9.25 (s, 1H), 10.60 (s, 1H).

TLC: R_f = 0.3 (97% dichloromethane:3% MeOH)

Example 31

5-{2-isoButoxy-5-[2-(4-morpholinyl)acetyl]-3-pyridinyl}-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-[5-(2-Chloroacetyl)-2-isobutoxy-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 30) (100 mg, 0.24 mmol), triethylamine (0.04 mL, 0.29 mmol) and morpholine (0.023 mL, 0.26 mmol) were stirred in dichloromethane (3 mL) under a nitrogen atmosphere for 16 h. The mixture was poured into ethyl acetate and washed with saturated sodium bicarbonate solution. The organics were dried ($MgSO_4$) and concentrated. The product was purified by flash column chromatography (eluting with 97% dichloromethane:3% methanol) to give 80 mg of product as a beige foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.15 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 2.60 m, 4H), 3.00 (t, 2H), 3.80 (m, 6H), 4.05 (s, 3H), 4.40 (d, 2H), 9.00 (s, 1H), 9.40 (s, 1H), 10.60 (s, 1H).

TLC: R_f = 0.3 (97% dichloromethane:3% MeOH)

Example 32

5-{5-[2-(4-Ethyl-1-piperazinyl)acetyl]-2-isobutoxy-3-pyridinyl}-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared as for Example 31.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (d, 6H), 1.10 (t, 3H), 1.80 (m, 2H), 2.25 (m, 1H), 2.40 (q, 2H), 2.40 -2.70 (m, 8H), 3.00 (t, 2H), 3.75 (s, 2H), 4.10 (s, 3H), 4.40 (d, 2H), 9.00 (s, 1H), 9.35 (s, 1H), 10.60 (s, 1H).

LRMS (ES): 409.0 (MH^+).

Example 29

5-(5-Glycoloyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Ethynyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 27) (1 g, 2.7 mmol) and $PhI(O_2CCF_3)_2$ (2.59 g, 6.02 mmol) were vigorously stirred in a mixture of dichloromethane: acetonitrile : H_2O (45 mL of 80:10:1) under a nitrogen atmosphere. After 10 h the mixture was cooled, diluted with dichloromethane and washed with saturated sodium bicarbonate. The organic layer was dried ($MgSO_4$) and evaporated to give the crude product. Flash column chromatography (95% dichloromethane:methanol) gave 300 mg of pure product and a further 300 mg of slightly impure product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 3,00 (t, 2H), 3.40 (t, 1H), 4.05 (s, 3H), 4.45 (d, 2H), 4.90 (d, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).

TLC: R_f = 0.3 (95% dichloromethane:5% MeOH).

Example 30

5-[5-(2-Chloroacetyl)-2-isobutoxy-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Glycoloyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 29) (0.3 g, 0.75 mmol), triethylamine (0.14 mL, 0.98 mmol) and methanesulfonyl chloride (0.07 mL, 0.9 mmol) were stirred in dichloromethane (7 mL) at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organics were dried ($MgSO_4$) and evaporated. The product was purified by flash

mixture partitioned between 3% sodium bicarbonate solution and ethyl acetate. The organics were concentrated and redissolved in acetonitrile. Tetraethylammonium fluoride (1.27 g, 8.52 mmol) was added and the mixture stirred for 1.5 h at room temperature. A further portion of tetraethylammonium fluoride was added and the mixture stirred for a further 1.5 h. The organics were evaporated and the crude mixture partitioned between 3% sodium bicarbonate solution and ethyl acetate. The organics were dried ($MgSO_4$) and concentrated to give the product as a fawn solid (2.35 g)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H, 1.80 (m, 2H), 2.30 (m, 1H), 3.00 (t, 2H), 3.20 (s, 1H), 4.05 (s, 3H), 4.35 (d, 2H), 8.40 (s, 1H), 8.80 (s, 1H).

TLC (1:1 ethyl acetate/pentane): R_f = 0.25

Example 28

5-[2-Isobutoxy-5-(1*H*-1,2,3-triazol-5-yl)-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Ethynyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 27) (200 mg, 0.54 mmol) and trimethylsilylazide (630 mg, 5.4 mmol) were stirred at 170°C in a sealed pressure vessel for 14 h. The reaction mixture was cooled and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The brown precipitate was filtered off and the 2 phases separated. The organic phase was washed with more sodium bicarbonate solution and brine, dried with ($MgSO_4$) and concentrated. This residue was combined with the original precipitate and purified by flash column chromatography (gradient elution from dichloromethane to 5% methanol: dichloromethane) to give 109 mg of a white solid (49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3H), 1.00 (d, 6H), 1.75 (m, 2H), 2.20 (m, 1H), 2.90 (t, 2H), 4.00 (s, 3H), 4.30 (d, 2H), 7.80 (s, 1H), 8.60 (s, 1H), 9.00 (s, 1H), 10.80 (s, 1H).

diluted with further dichloromethane and washed with a 1 *N* solution of citric acid, followed by brine. The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was redissolved in dichloromethane and thionyl chloride (0.05 mL, 0.62 mmol) was added. After 2 h the solution was washed with water then sodium bicarbonate solution. The organic phase was dried and concentrated. The crude residue was purified by flash column chromatography (50% ethyl acetate:pentane as eluant) to give the product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, 6H), 1.05 (t, 3H), 1.40 (s, 6H), 1.80 (m, 2H), 2.00 (m, 1H), 3.10 (t, 2H), 4.10 (s, 2H), 4.20 (d, 2H), 4.25 (s, 3H), 8.60 (s, 1H), 8.75 (s, 1H).

LRMS (TSP): 439.0 (MH^+).

Example 26

6-Isobutoxy-*N*,*N*-dimethyl-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)nicotinamide

The title compound was made by the method of Example 5 using the title compound of Example 24.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 2.95 (t, 2H), 3.20 (br s, 6H), 4.00 (s, 3H), 4.40 (d, 2H), 8.40 (s, 1H), 8.90 (s, 1H), 10.75 (s, 1H).

LRMS (TSP): 413.3 (MH^+).

Example 27

5-(5-Ethynyl-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Iodo-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 22) (3 g, 6.42 mmol), trimethylsilylacetylene (4.5 mL, 32.1 mmol), copper(I) iodide (37 mg, 0.19 mmol), Pd $(PPh_3)_2Cl_2$ (13.5 mg, 0.19 mmol) were stirred together in a mixture of acetonitrile (50 mL) and triethylamine (50 mL) at 40°C for 16 h under a nitrogen atmosphere. The solvent was evaporated and the crude

Methyl 6-isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl)nicotinate

The title compound was made by the method of Example 2 using the title compound of Example 22.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.15 (d, 6H), 1.80 (m, 2H), 2.30 (m, 1H), 3.00 (t, 2H), 4.00 (s, 3H), 4.10 (s, 3H), 4.40 (d, 2H), 8.80 (s, 1H), 9.30 (s, 1H), 10.65 (s, 1H).

LRMS (TSP): 400.1 (MH^+).

Example 24

6-Isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)nicotinic acid

The title compound was made by the method of Example 3 using the title compound of Example 23.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.25 (m, 1H), 3.05 (t, 2H), 4.10 (s, 3H), 4.40 (d, 2H), 8.95 (s, 1H), 9.20 (s, 1H), 11.10 (br s, 1H).

LRMS (TSP): 386.1 (MH^+).

Example 25

5-[5-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2-isobutoxy-3-pyridinyl]-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

6-Isobutoxy-5-(2-methyl-7-oxo-3-propyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]-pyrimidin-5-yl)nicotinic acid (Example 24) (200 mg, 0.52 mmol) was dissolved in dichloromethane and oxalyl chloride (0.18 mL, 2.8 mmol) was added followed by 1 drop of *N*,*N*-dimethylformamide. The mixture was stirred for 2 h and the solvent was then removed *in vacuo*, azeotroping with further dichloromethane. A dichloromethane solution of the acid chloride was then added to a solution of 2-amino-2-methyl-1-propanol (0.05 mL, 0.52 mmol) and diisopropylethylamine (0.09 mL, 0.62 mmol) in dichloromethane and the mixture stirred for 2 h. The reaction mixture was

Example 20b

5-(2-Butoxy-5-ethynyl-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 15 using the title compound of Example 20a.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 3.20 (s, 1H), 3.35 (s, 3H), 3.80 (t, 2H), 4.60 (t, 2H), 4.80 (t, 2H), 8.40 (s, 1H), 8.85 (s, 1H), 11.00 (s, 1H).

LRMS (TSP): 396.4 (MH^+).

Example 21

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 16 using the title compound of Example 20.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 2.60 (s, 3H), 3.00 (q, 2H), 3.30 (s, 3H), 3.80 (t, 2H), 4.60 (t, 2H), 4.75 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.90 (s, 1H).

LRMS (TSP): 413.9 (MH^+).

Example 22

5-(5-Iodo-2-isobutoxy-3-pyridinyl)-2-methyl-3-propyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 1 using the title compound of Preparation 14.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.10 (d, 6H), 1.80 (m, 2H), 2.25 (m, 1H), 3.00 (t, 2H), 4.05 (s, 3H), 4.30 (d, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 468.1 (MH^+).

Example 23

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 3.35 (s, 3H), 3.85 (t, 2H), 4.60 (t, 2H), 4.80 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 11.00 (s, 1H).

LRMS (TSP): 467.5 (MH^+).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.95 (m, 2H), 2.35 (s, 6H), 2.80 (t, 2H), 3.10 (q, 2H), 3.20 (t, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.45 (t, 2H), 4.65 (t, 2H), 8.80 (s, 1H), 9.25 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 471.3 (MH^+).

Example 19

5-{2-Butoxy-5-[3-(4-ethyl-1-piperazinyl)propanoyl]-3-pyridinyl}-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was prepared by the method of Example 18

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.95 (m, 2H), 2.40 (q, 2H), 2.40-2.70 (m, 8H), 2.85 (t, 2H), 3.10 (q, 2H), 3.20 (t, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.70 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 540.1 (MH^+).

Example 20

5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 1 using the title compound of Preparation 15.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.95 (m, 2H), 3.00 (q, 2H), 3.35 (s, 3H), 3.85 (t, 2H), 4.60 (t, 2H), 4.80 (t, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.95 (s, 1H).

LRMS (TSP): 497.8 (MH^+).

Example 20a (Preparative example)

5-(2-Butoxy-5-trimethylsilylethynyl-3-pyridinyl)-3-ethyl-1-(2-methoxyethyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound was made by the method of Example 14 using the title compound of Example 20.

for 5 minutes to degas the solution. After cooling potassium hexamethyldisilazide (360 mg, 1.80 mmol) was added and the solution reheated to reflux for 8 h. The cooled reaction mixture was evaporated to dryness and partitioned between ethyl acetate and water after 1N hydrochloric acid had been used to adjust the pH to 8. The organic phase was separated and washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (gradient elution from 100% dichloromethane : 0.5% ammonia to 99% dichloromethane : 1% methanol : 0.5% ammonia) to give the title compound (45 mg, 29%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, 3H), 1.50 (d, 3H), 2.60 (s, 3H), 3.10 (q, 2H), 3.30 (s, 3H), 3.50 (s, 3H), 3.60-3.80 (m, 2H), 3.90 (t, 2H), 4.40 (t, 2H), 5.60 (m, 1H), 8.80 (s, 1H), 9.10 (s, 1H), 10.80 (s, 1H).

LRMS (TSP): 430.3 (MH^+).

Example 18

5-{2-Butoxy-5-[3-(dimethylamino)propanoyl]-3-pyridinyl}-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Dimethylamine hydrochloride (280 mg, 31 mmol) was added to formaldehyde (72 mg, 2 mL of a 37-41% aqueous solution) and the mixture sonicated until the white solid dissolved. After 30 min acetic anhydride (1.2 mL) was added and the mixture warmed in a water bath until a clear solution was obtained. A portion of this solution (0.16 mL) was added to 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 16) (100 mg, 0.24 mmol) and the resulting solution heated in a water bath. After 1 h the reaction was cooled and extracted from saturated sodium bicarbonate solution with ethyl acetate. The organics were washed with a further portion of sodium bicarbonate solution then brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (gradient elution from 100% dichloromethane to 10% methanol: dichloromethane) to give 50 mg product.

layer was dried ($MgSO_4$) and concentrated to give the title compound as a white solid (75 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 3.05 (q, 2H), 3.20 (s, 1H), 3.30 (s, 3H), 3.85 (t, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 396.3 (MH^+).

Example 16

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound of Example 15 (2.4 g, 6 mmol) and mercury sulfate (100 mg, 0.34 mmol) were stirred together in a mixture of 1N H_2SO_4 (5 mL) and acetone (35 mL). After 2 h a further portion of mercury sulfate (100 mg) was added and a third portion (100 mg in 5 mL 1N H_2SO_4) was added 2 h later. The crude reaction mixture was concentrated and the black residue partitioned between dichloromethane and water. The organic phase was separated and washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated. Purification by flash column chromatography (gradient elution from 30% ethyl acetate: pentane to 100% ethyl acetate) gave 780 mg product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.95 (m, 2H), 2.60 (s, 3H), 3.10 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.45 (t, 2H), 4.65 (t, 2H), 8.80 (s, 1H), 9.20 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 414.3 (MH^+).

Example 17

5-[5-Acetyl-2-(2-methoxy-1-methylethoxy)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 16) (150 mg, 0.36 mmol) was dissolved in 1-methoxypropan-2-ol (3 mL) and the solution heated at reflux

LRMS (ES): 449.2 (MH^+).

Example 14 (Preparative example)

5-(2-Butoxy-5-trimethylsilylethynyl-3-pyridinyl)-3-ethyl-2-(2-methoxy-ethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

The title compound from Example 1 (127 mg, 0.25 mmol) was suspended in triethylamine (2 mL) and trimethylsilylacetylene (38 mg, 0.39 mmol) and acetonitrile (2 mL to try and solubilise reactants). $Pd(PPh_3)_2Cl_2$ (5 mg, 0.006 mmol) and cuprous iodide (1.2 mg, 0.006 mmol) were added and the reaction mixture stirred. After 1 h a further portion of trimethylsilylacetylene (19 mg, 0.19 mmol) was added and stirring continued for 2 h. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organics were washed with brine, dried ($MgSO_4$) and concentrated to give a brown foam. Purification by flash column chromatography (gradient elution from 100% dichloromethane to 99% dichloromethane/methanol) gave the title compound as a light brown solid (108 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9H), 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 3.10 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 468.3 (MH^+).

Example 15

5-(2-Butoxy-5-ethynyl-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Potassium fluoride (22 mg, 0.38 mmol) was added to a stirred solution of the title compound from Example 14 (90 mg, 0.19 mmol) in aqueous *N,N*-dimethylformamide (2 mL *N,N*-dimethylformamide /0.2 mL water) at 0°C. After 10 min the reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water, 1 *N* hydrochloric acid (3 times) and brine. The organic

residue triturated with ethyl acetate to give an orange solid. Purification by flash column chromatography (elution with 50:1 dichloromethane / methanol) gave the title compound as a cream solid (121 mg, 58%).

MP = 154-155°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.95 (m, 2H), 3.05 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 6.50 (s, 1H), 6.70 (s, 1H), 7.50 (s, 1H), 8.60 (s, 1H), 9.00 (s, 1H), 10.80 (s, 1H).

LRMS (ES): 438.1 (MH^+).

Example 13

5-(2-Butoxy-5-[2-pyridyl]-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

2-Tributyltin pyridine (192 mg, 0.52 mmol), lithium chloride (170 mg, 4.00 mmol), cuprous iodide (11.5 mg, 0.06 mmol), $Pd(PPh_3)_4$ (46.5 mg, 0.04 mmol) and the title compound of Example 1 (200 mg, 0.40 mmol) were stirred together in dioxan (10 mL) under a nitrogen atmosphere. The mixture was heated at reflux for 3.5 h, allowed to cool and the solvent removed *in vacuo*. The residue was taken up in ethyl acetate and shaken vigorously with 5% aqueous potassium fluoride solution for 10 min and the mixture filtered through Arbocel®. The organic layer was separated, washed with 5% aqueous potassium fluoride solution, saturated sodium bicarbonate solution and brine. The organics were dried ($MgSO_4$) and concentrated. The solid was partially purified by trituration with cold ethyl acetate and further purified by flash column chromatography (elution with 50:1 dichloromethane/methanol) to give the title compound (52 mg, 29%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.95 (m, 2H), 3.10 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.45 (t, 2H), 4.60 (t, 2H), 7.30 (m, 1H), 7.80 (m, 2H), 8.75 (d, 1H), 8.90 (s, 1H), 9.30 (s, 1H), 10.80 (s, 1H).

Example 11

5-[2-Butoxy-5-[3-(trifluoromethyl)phenyl]-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 1) (140 mg, 0.28 mmol), K_2CO_3 (78 mg, 0.56 mmol) and 3-trifluoromethylboronic acid (60 mg, 0.34 mmol) were stirred together in aqueous dioxan under a nitrogen atmosphere. The mixture was immersed in a pre-heated oil bath at 120°C for a few minutes and $Pd(PPh_3)_4$ (34 mg, 0.028 mmol) was added. The mixture was heated at reflux for 2 h and then cooled. The cooled mixture was concentrated and partitioned between ethyl acetate and water. This was then filtered through an Arbocel® pad to remove the palladium residues and the organic layer separated, washed with sodium bicarbonate solution then brine, dried ($MgSO_4$) and concentrated. Recrystallisation from ethyl acetate gave the title compound (101 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 2.00 (m, 2H), 3.05 (q, 2H), 3.25 (s, 3H), 3.90 (t, 2H), 4.45 (t, 2H), 4.65 (t, 2H), 7.60 (m, 2H), 7.80 (d, 1H), 7.85 (s, 1H), 8.50 (s, 1H), 8.95 (s, 1H), 10.85 (s, 1H).

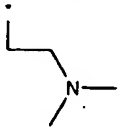
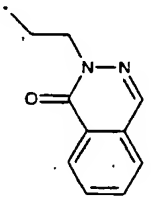
LRMS (ES): 516.1 (MH^+).

Analysis: found C, 60.21; H, 5.43; N,13.48; $C_{26}H_{28}N_5O_5F_3$ requires C, 60.57; H, 5.47; N, 13.58.

Example 12

5-[2-Butoxy-5-(2-furyl)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

$Pd(PPh_3)_4$ (46.5 mg, 0.04 mmol) was added to a stirred mixture of potassium carbonate (55 mg, 0.40 mmol), 2-furylboronic acid (54 mg, 0.48 mmol) and the title compound of Example 1 (200 mg, 0.40 mmol) in degassed dioxan / water (10 mL of 4:1 mixture). The mixture was heated at reflux for 2 h and cooled. The solvent was removed *in vacuo* and the

9[4]		500.5	(300 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 3.00 (s, 3H), 3.05 (q, 2H), 3.0-3.1 (m, 2H), 3.20 (s, 3H), 3.30 (s, 3H), 3.45 (m, 2H), 3.80 (t, 2H), 3.90 (m, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.40 (s, 1H), 8.80 (s, 1H), 12.0 (br s, 1H).
10[5]		601.7	(300 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.85 (m, 2H), 2.60 (br s, 2H), 2.90-3.30 m, 4H), 3.30 (s, 3H), 3.90-4.10 (m, 4H), 4.40 (t, 2H), 4.60 (br s, 3H), 7.40-8.30 (m, 5H), 8.40 (s, 1H), 8.80 (s, 1H), 10.75 (br s, 1H).

1 = *N*-{4-[2-(methylamino)ethyl]phenyl}methanesulfonamide (EP 245 997) was the amine used

2 = 2-(2-methylaminoethyl)pyridine was the amine used

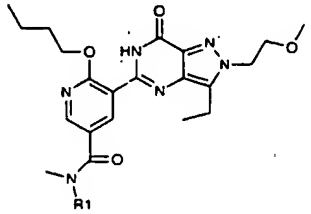
3 = 2,3-dihydro-1,4-benzodioxin-2-yl-*N*-methylmethanamine (Gazz. Chim. Ital. 83; 1953; 144; 148) was the amine used.

4 = *N*,*N*,*N*'-trimethylethylenediamine was the amine used.

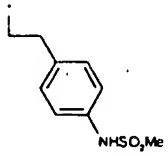
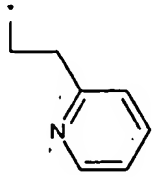
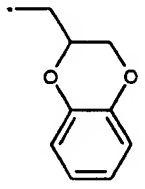
5 = 2-[2-(methylamino)ethyl]-1-(2*H*)-phthalazinone (EP 242 173) was the amine used.

Examples 6 to 10

The following compounds were made by the same method as Example 5



from the compound of Example 3 and the appropriate amine.

Ex.	R1	LRMS (MH)$^+$	^{1}H NMR
6[1]		626.7	(300 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.40 (m, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.80-3.20 (m, 10H), 3.30 (s, 3H), 3.40-3.80 (m, 2H), 3.85 (t, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 6.80-9.80 (m, 7H), 10.80 (s, 1H).
7[2]		534.5	(300 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 3.20 (s, 3H), 3.25 (s, 3H), 3.50 (m, 2H), 3.80 (t, 2H), 3.90 (m, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 7.70 (m, 1H), 7.80 (m, 1H), 8.25 (m, 2H), 8.80 (m, 2H).
8[3]		577.7	(300 MHz, $CDCl_3$) δ:1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 3.00 (q, 2H), 3.20 (s, 3H), 3.30 (s, 3H), 3.70 (m, 1H), 3.80 (t, 2H), 4.10 (m, 2H), 4.40 (m, 1H), 4.45 (m, 3H), 4.60 (t, 2H), 6.95 (m, 4H), 8.40 (s, 1H), 8.80 (s, 1H), 10.75 (s, 1H).

Example 5

6-Butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]-*N*-methoxy-*N*-methylnicotinamide

6-Butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo-[4,3-*d*]pyrimidin-5-yl]nicotinic acid (Example 3) (200 mg, 0.48 mmol) was dissolved in dichloromethane and 1-hydroxybenzotriazole hydrate (78 mg, 0.58 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (120 mg, 0.58 mmol) were added followed by diisopropylethylamine (0.34 mL, 1.95 mmol). *N,O*-dimethylhydroxyl-amine hydrochloride (56.3 mg, 0.58 mmol) was added and the mixture stirred at room temperature for 14 h. A further 0.29 mmol of 1-hydroxy-benzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride were added and the reaction stirred for a further 3 h. The reaction mixture was diluted with further dichloromethane, washed with water, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (gradient elution from dichloromethane to 5% methanol: dichloromethane) gave the title compound (178 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.60 (m, 2H), 1.95 (m, 2H), 3.05 (q, 2H), 3.25 (s, 3H), 3.40 (s, 3H), 3.60 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.60 (t, 2H), 8.65 (s, 1H), 9.20 (s, 1H), 10.75 (s, 1H).

LRMS (TSP): 459.7 (MH^+)

Analysis: found C, 57.80; H, 6.56; N, 18.02; $C_{22}H_{30}N_6O_5$ requires C, 57.63; H, 6.59; N, 18.33.

Example 4

5-[2-Butoxy-5-(hydroxymethyl)-3-pyridinyl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Carbonyldiimidazole (47 mg, 0.24 mmol) was added to a stirred solution of 6-butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]nicotinic acid (Example 3) (100 mg, 0.24 mmol) in tetrahydrofuran (3 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. A further 20 mg of carbonyldiimidazole was added and the mixture stirred for a further 1 h. The mixture was cooled to 0°C and water (0.3 mL) added followed by sodium borohydride (27.4 mg, 0.72 mmol). Stirring was continued for 1 h. The reaction mixture was quenched with water and extracted from 2 *N* HCl with ethyl acetate. The organic fractions were washed with brine, dried ($MgSO_4$) and evaporated to give the crude product. The crude product was purified by flash column chromatography (gradient elution from dichloromethane to 5% methanol: dichloromethane) to give the title compound (20 mg, 21%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.20 (br s, 1H), 3.05 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.55 (t, 2H), 4.75 (s, 2H), 8.20 (s, 1H), 8.80 (s, 1H), 10.80 (s, 1H).

LRMS (TSP): 402.4 (MH^+)

Analysis: found C, 59.06; H, 6.79; N, 17.01; $C_{20}H_{27}N_5O_4 0.3H_2O$ requires C, 59.04; H, 6.84; N, 17.21.

flash column chromatography (gradient elution from dichloromethane to 2% methanol: dichloromethane) to give the title compound (89 mg, 100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 3.05 (q, 2H), 3.25 (s, 3H), 3.90 (t, 2H), 4.00 (s, 3H), 4.40 (t, 2H), 4.60 (t, 2H), 8.85 (s, 1H), 9.25 (s, 1H), 10.60 (s, 1H).

LRMS (TSP): 430.2 (MH^+).

Example 3

6-Butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]nicotinic acid

Sodium hydroxide (0.52 mL of 2N) was added to a solution of methyl 6-butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]nicotinate (Example 2) (226 mg, 0.53 mmol) in dioxane. The solution was stirred for 14 h. The pH was adjusted to pH 2-3 with hydrochloric acid (1N) and the mixture concentrated to dryness. Hot ethanol was added to the solid and the slurry filtered. The ethanol solution was concentrated and the resulting solid was washed with dichloromethane resulting in the title compound (156 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 3.10 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.55 (t, 2H), 4.65 (t, 2H), 8.95 (s, 1H), 9.25 (s, 1H), 10.90 (s, 1H).

LRMS (TSP): 416.5 (MH^+).

Synthesis of the Compounds of Formulae IA and IB

Example 1

5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

Potassium hexamethyldisilazide (46 mg, 0.23 mmol) was added to *N*-[3-(aminocarbonyl)-5-ethyl-1-(2-methoxyethyl)-1*H*-pyrazol-4-yl]-2-butoxy-5-iodonicotinamide (Preparation 13) (100 mg, 0.19 mmol) in degassed n-butanol (2 mL) and the solution stirred under a nitrogen atmosphere. The reaction was heated at reflux for 9 h and then cooled. The butanol was removed *in vacuo* and the residue partitioned between dichloromethane and 1N hydrochloric acid. The organic phase was separated and washed with brine, dried ($MgSO_4$) and concentrated to give a white solid. Trituration with ethyl acetate gave the title compound (40 mg, 42%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.40 (t, 3H), 1.55 (m, 2H), 1.90 (m, 2H), 3.05 (q, 2H), 3.30 (s, 3H), 3.90 (t, 2H), 4.40 (t, 2H), 4.55 (t, 2H), 8.40 (s, 1H), 9.00 (s, 1H), 10.70 (s, 1H).

LRMS (TSP): 498.1 (MH^+).

Example 2

Methyl 6-butoxy-5-[3-ethyl-2-(2-methoxyethyl)-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]nicotinate

5-(2-Butoxy-5-iodo-3-pyridinyl)-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Example 1) (100 mg, 0.20 mmol), palladium acetate (31.6 mg, 0.141 mmol), 1,2-bis(diphenylphosphino)-propane (37 mg, 0.09 mmol) and triethylamine (0.22 mL, 1.56 mmol) were added to methanol (5 mL) and dimethylsulfoxide (0.7 mL). The reagents were stirred together under an atmosphere of carbon monoxide (482.6 kPa (70 psi)) at 75°C for 14 h. The reaction mixture was filtered through Celite® and the solvent removed *in vacuo*. The product was purified by

9.03 (s, 1H), 10.49 (bs, 1H)

LRMS (ES - positive) 529 (MH^+)

Anal. Found C, 58.04; H, 6.85; N, 15.39. Calcd for $C_{26}H_{36}O_6N_6.0.5H_2O$: C, 58.09; H, 6.94; N, 15.63.

Preparation 63

5-Acetyl-*N*-{5-(aminocarbonyl)-3-ethyl-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-1*H*-pyrazol-4-yl}-2-ethoxynicotinamide

The title compound was prepared by the method of preparation 13 using 4-amino-3-ethyl-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-1*H*-pyrazole-5-carboxamide (prepared as in WO 9954333) and the title compound of preparation 59.

1H NMR (400MHz, $CDCl_3$): δ = 1.25 (m, 6H), 2.60 (s, 3H), 2.70 (q, 2H), 3.95 (s, 3H), 4.80 (q, 2H), 5.60 (s, 2H), 5.80 (br s, 1H), 6.85 (s, 1H), 6.90 (s, 1H), 8.90 (s, 1H), 9.00 (s, 1H), 9.80 (br s, 1H), 10.20 (s, 1H).

LRMS (ES - positive) 440 (MH^+); (ES – negative) 438 (ES^-)

Preparation 64

4-{[1-(5-Iodo-2-isobutoxy-3-pyridinyl)vinyl]amino}-1-methyl-5-propyl-1*H*-pyrazole-3-carboxamide

The title compound was prepared by the method of preparation 13 using the products of preparations 3 and 9.

1H NMR (300 MHz, $CDCl_3$): δ = 0.9 (3H, t), 1.0 (6H, t), 1.5-1.65 (2H, m), 2.2-2.45 (1H, m), 2.82 (2H, t), 3.85 (3H, s), 4.35 (2H, d), 5.2 (1H, br s), 6.6 (1H, br s), 8.4 (1H, d), 8.75 (1H, d), 10.2(1H, br s).

LRMS (TSP) 486 (MH^+).

1H NMR (400MHz, DMSO): δ = 1.12 (t, 3H), 1.42 (t, 3H), 2.58 (s, 3H), 2.73 (q, 2H), 4.61 (q, 2H), 7.26 (bs, 1H), 7.48 (bs, 1H), 8.72 (s, 1H), 8.90 (s, 1H), 10.52 (bs, 1H), 12.93 (bs, 1H).

LRMS (TSP - positive) 346.2 (MH^+)

Anal. Found C, 55.45; H, 5.64; N, 19.91. Calcd for $C_{16}H_{19}O_4N_5$: C, 55.65; H, 5.55; N, 20.28.

Preparation 62

tert-Butyl 4-[4-{[(5-acetyl-2-ethoxy-3-pyridinyl)carbonyl]amino}-3-(aminocarbonyl)-5-ethyl-1*H*-pyrazol-1-yl]-1-piperidinecarboxylate

The title compound from preparation 61 (4.32 g, 12.5 mmol) and cesium carbonate (4.90 g, 15.0 mmol) were dissolved in DMF (60 ml), and 1-(*tert*-butoxycarbonyl)-4-piperidinylmethane sulphonate (Bioorg. Med. Chem. Lett. 1999, 9, 1285) (4.20 g, 15.0 mmol) was added in one portion. The mixture was stirred at 100°C under nitrogen for 6h, after which additional 1-(*tert*-butoxycarbonyl)-4-piperidinylmethane sulphonate (1.75 g, 6.26 mmol) and cesium carbonate (2.00 g, 6.26 mmol) were added. The mixture was heated at 60°C for a further 16 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate (200 ml) and water (200 ml). Brine (50 ml) was then added, the organic layer separated and the aqueous extracted further with ethyl acetate (2 x 100 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by column chromatography (first with 98:2 methylene chloride_methanol; and repeated with 1:1 to 0:1 pentane:ethyl acetate) to yield the title compound as a white solid (3.8 g, 7.19 mmol).

m.p. 197-202°C

1H NMR (400MHz, $CDCl_3$): δ = 1.24 (t, 3H), 1.49 (s, 9H), 1.58 (t, 3H), 1.92 (m, 2H), 2.15 (m, 2H), 2.60 (s, 3H), 2.90 (m, 2H), 2.93 (q, 2H), 4.22 (m, 1H), 4.29 (m, 2H), 4.78 (q, 2H), 5.26 (bs, 1H), 6.66 (bs, 1H), 8.88 (s, 1H),

ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a beige solid. This was recrystallised from isopropyl alcohol to yield the title compound as a pale brown solid (1.1 g, 2.75 mmol)

m.p. 238-240°C

1H NMR (400MHz, $CDCl_3$): δ = 0.39 (m, 2H), 0.60 (m, 2H), 1.18 (t, 3H), 1.26 (m, 1H), 1.53 (t, 3H), 2.58 (s, 3H), 2.92 (q, 2H), 3.95 (d, 2H), 4.74 (q, 2H), 5.26 (br s, 1H), 6.64 (br s, 1H), 8.85 (s, 1H), 9.00 (s, 1H), 10.48 (br s, 1H).

LRMS (ES - positive) 400 (MH^+)

Anal. Found C, 59.34; H, 6.41; N, 16.80. Calcd for $C_{20}H_{25}O_4N_5.0.3H_2O.0.2IPA$: C, 59.35; H, 6.58; N, 16.80.

Preparation 61

5-Acetyl-*N*-[3-(aminocarbonyl)-5-ethyl-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide

A solution of the title compound from preparation 59 (5.70 g, 27.3 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*–tetramethyluronium hexafluorphosphate (10.9g, 28.6 mmol) in methylene chloride (100 ml) was added to a solution of 4-amino-3-ethyl-1*H*-pyrazole-5-carboxamide (prepared as WO 98/49166) (4.20 g, 27.3 mmol) and diisopropylethylamine (23.7 ml, 136.2 mmol) in methylene chloride (115 ml). After 1h the mixture was diluted with brine (100 ml) and washed with $NaHCO_3$ (sat. aq., 100 ml) and then HCl (2N, 100 ml). Each aqueous layer was back-extracted with dichloromethane (100 ml), and the combined organics washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. An analytical sample of the title compound was obtained by trituration with ethyl acetate, followed by recrystallisation from ethanol, while the remainder was purified by flash column chromatography (95:5 methylene chloride : methanol as eluent) to yield the title compound (total weight = 7.8 g, 22.5 mmol).

m.p. 217-219°C

Preparation 59

5-Acetyl-2-ethoxynicotinic acid

To a solution of the title compound of preparation 58 (7.15 g, 32.0 mmol) in dioxane (50 ml) was added a solution of sodium hydroxide (2.56 g, 64.1 mmol) in water (10 ml). The mixture was stirred at RT for 2h, after which it was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The aqueous layer was separated, acidified with 2N HCl, and then extracted with ethyl actetate (3 x 100 ml). These combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a yellow solid (6 g, 28.6 mmol).

m.p. 117-118°C

1H NMR (300MHz, $CDCl_3$): δ = 1.54 (t, 3H), 2.62 (s, 3H), 4.78 (q, 2H), 8.95 (br s, 2H)

LRMS (ES - negative) 208 (MH^-)

Anal. Found C, 57.32; H, 5.43; N, 6.53. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70.

Preparation 60

5-Acetyl-*N*-[3-(aminocarbonyl)-1-(cyclopropylmethyl)-5-ethyl-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide

A solution of the title compound of preparation 56 (800 mg, 3.82 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorphosphate (1.59 g, 4.40 mmol) in DMF (30 ml) was added to a solution of the title compound of preparation 55 (796 mg, 3.82 mmol) and diisopropylethylamine (3.33 ml, 19.1 mmol) in DMF (15 ml). After 1h the DMF was removed *in vacuo*, and the residue was partitioned between ethyl actetate (200 ml) and water (200 ml). The organic layer was separated, washed with $NaHCO_3$ (sat. aq., 100 ml) and 1N HCl (aq., 100

layer was dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound as an off-white solid (34 g, 111 mmol).

m.p. 67-69°C

1H NMR (400MHz, $CDCl_3$): δ = 1.41 (t, 3H), 3.90 (s, 3H), 4.43 (q, 2H), 8.36 (s, 1H), 8.44 (s, 1H)

LRMS (TSP - positive) 308 (MH^+)

Anal. Found C, 35.06; H, 3.18; N, 4.45. Calcd for $C_9H_{10}O_3NI$: C, 35.20; H, 3.28; N, 4.56.

Preparation 58

Methyl 5-acetyl-2-ethoxynicotinate

Palladium (II) acetate (877 mg, 3.90 mmol), butyl vinyl ether (19.8 ml, 0.15 mol) and tri-*o*-tolyl phosphine (2.37 g, 7.81 mmol) were added to a stirring solution of the title compound of preparation 57 (15.0 g, 48.8 mmol) and triethylamine (10.9 ml, 78.1 mmol) in acetonitrile (150 ml). The mixture was refluxed for 1.5h under nitrogen, and then the solvent removed *in vacuo*. The residue was taken up in 6N HCl (60 ml), and stirred at RT for 1h. The mixture was then diluted with water, and extracted with ethyl acetate (3 x 250 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The brown residue was purified by flash column chromatography (methylene chloride as eluent) to give an off-white solid, which was recrystallised from diisopropylether to yield the title compound as pale brown needles (5.3 g, 23.7 mmol).

m.p. 111-112°C

1H NMR (400MHz, $CDCl_3$): δ = 1.41 (t, 3H), 2.56 (s, 3H), 3.89 (s, 3H), 4.54 (q, 2H), 8.62 (s, 1H), 8.83 (s, 1H)

LRMS (TSP - positive) 224 (MH^+)

Anal. Found C, 59.11; H, 5.80; N, 6.22. Calcd for $C_{11}H_{13}O_4N$: C, 59.19; H, 5.87; N, 6.27.

stirred solution of the title compound of preparation 37 (15.0 g, 51.2 mmol) and triethylamine (10.5 ml, 81.9 mmol) in acetonitrile (150 ml). The mixture was refluxed for 3h under nitrogen, and then stirred at RT for 16h. The solvent was removed *in vacuo*, and the residue taken up in 6N HCl (80 ml), and stirred at RT for 40 min. The mixture was then diluted with water and ethyl acetate, filtered through Arbocel® and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3 x 200 ml), and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then taken up in $NaHCO_3$ (sat. aq., 500 ml) and ethyl acetate (200 ml). The organic layer was separated, the aqueous layer washed with dichloromethane (200 ml), acidified with conc. HCl to pH 1, and extracted with ethyl acetate (5 x 200 ml). The combined extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude product by column chromatography (99:1:0.25 ethyl acetate:methanol:acetic acid as eluent), and then recrystallisation from hot diisopropylether gave the title compound as a yellow solid (3.91 g, 18.9 mmol).

1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (t, 3H), 2.60 (s, 3H), 4.80 (q, 2H), 8.93 (s, 1H), 8.96 (s, 1H).

LRMS (ES - negative) 208 (MH^-)

Preparation 57

Methyl 2-ethoxy-5-iodonicotinate

Concentrated sulphuric acid (2 ml) was added to a stirring suspension of the title compound of preparation 37 (40 g, 137 mmol) in methanol (250 ml), and the mixture refluxed for 2h. A further aliquot of sulphuric acid (1 ml) was added, and the mixture refluxed for a further 2h, before standing at –18°C for 16h. The off-white precipitate was filtered off and washed with methanol, dissolved in ethyl acetate (500 ml) and the solution, washed with $NaHCO_3$ (sat. aq., 200 ml) and brine (200 ml). The organic

3H), 1.3 (m, 1H), 2.9 (q, 2H), 4.2 (d, 2H), 6.0 (br s, 1H), 7.15 (br s, 1H).

LRMS (TSP) 239 (MH^+).

Analysis: Found C, 50.38; H, 5.93; N, 23.12. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52%

1-(cyclopropylmethyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide

1H NMR (300 MHz, $CDCl_3$): δ = 0.35-0.41 (m, 2H), 0.6-0.65 (m, 2H), 1.25 (t, 3H), 1.2-1.3 (m, 1H), 2.95 (q, 2H), 4.0 (d, 2H), 5.85 (br s, 1H), 7.2 (br s, 1H).

LRMS (TSP) 239 (MH^+).

Analysis: Found C, 50.30; H, 5.90; N, 23.39. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52%

Preparation 55

4-Amino-1-(cyclopropylmethyl)-5-ethyl-1*H*-pyrazole-3-carboxamide

The title compound was prepared following the method of preparation 11 using 1-(cyclopropylmethyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide (from preparation 54b) in 92% yield (7.7 g).

m.p. 143-145°C.

1H NMR (400 MHz, $CDCl_3$): δ = 0.35-0.42 (m, 4H), 1.18 (t, 3H), 1.25-1.35 (m, 1H), 2.55 (q, 2H), 2.8 (br s, 2H), 4.33 (s, 1H), 4.36 (s, 1H).

LRMS (TSP) 209 (MH^+).

Analysis: Found C, 57.58; H, 7.78; N, 26.76. Calcd for $C_{10}H_{16}N_4O$: C, 57.67; H, 7.74; N, 26.91%

Preparation 56

5-Acetyl-2-ethoxynicotinic acid

Palladium (II) acetate (919 mg, 4.08 mmol), butyl vinyl ether (18.9 ml, 146.5 mmol) and tri-*o*-tolyl phosphine (2.50 g, 8.16 mmol) were added to a

Anal. Found C, 47.55; H, 5.71; N, 13.07 Calcd for $C_{25}H_{35}O_5N_6I.0.3H_2O$, C, 47.52; H, 5.68; N, 13.30

Preparation 54a

1-(cyclopropylmethyl)-3-ethyl-4-nitro-1*H*-pyrazole-5-carboxamide

and

Preparation 54b

1-(cyclopropylmethyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide

A suspension of 3-ethyl-4-nitro-1*H*-pyrazole-5-carboxamide (prepared as in WO98/49166) (40.0 g, 217 mmol) in dry DMF (300 ml) was treated with cesium carbonate (77.8 g, 239 mmol). To this, in a single portion, was added cyclopropylmethyl bromide (22.9 ml, 239 mmol) and the resultant suspension stirred at RT for 6h. After condensation *in vacuo*, the residue was partioned between ethyl acetate (200 ml) and water (200 ml), and the insoluble material removed by filtration. The solid was partioned between water (200 ml) and methylene chloride (200 ml), and undissolved solid removed by filtration. Combined organics were washed with brine (100 ml), dried over $MgSO_4$, and condensed to a solid (~40 g). The two regioisomers were separated by crystallisation of the crude mixture. The more lipophilic component (Rf = 0.27, methylene chloride:methanol 98:2) crystallising from a mixture of methylene chloride (50 ml) and diisopropylether (200 ml) to give 1-(cyclopropylmethyl)-3-ethyl-4-nitro-1*H*-pyrazole-5-carboxamide (12 g, 50 mmol). Crystallisation of the mother liquors from acetonitrile gave the more polar component (Rf = 0.19, methylene chloride:methanol 98:2) (10 g, 42 mmol) which was confirmed as the 1-(cyclopropylmethyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide by nOe experiements. The mother liquors contained further material as a mixture of regioisomers (20 g, 84 mmol).

1-(cyclopropylmethyl)-3-ethyl-4-nitro-1*H*-pyrazole-5-carboxamide

1H NMR (300 MHz, $CDCl_3$): δ = 0.38-0.42 (m, 2H), 0.5-0.6 (m, 2H), 1.2 (t,

1H NMR (400MHz, $CDCl_3$): δ = 1.00 (m, 6H), 1.90 (m, 2H), 2.80 (q, 2H), 4.50 (t, 2H), 5.20 (s, 1H), 5.40 (s, 2H), 6.60 (s, 1H), 6.90 (d, 1H), 7.20 (m, 1H), 7.60 (app. t, 1H), 8.40 (d, 1H), 8.60 (m, 1H), 8.75 (s, 1H), 10.40 (s, 1H)

LRMS (ES- positive ion) 535 (MH^+), (ES – negative ion) 533 (M-H)

Anal. Found C, 47.53; H, 4.41; N, 15.69. Calcd for $C_{21}H_{23}O_3N_6I$: C, 47.20; H, 4.34; N, 15.73.

Preparation 52

tert-Butyl 3-(3-(aminocarbonyl)-5-ethyl-4-{[(5-iodo-2-propoxy-3-pyridinyl)carbonyl]amino}-1*H*-pyrazol-1-yl)-1-azetidinecarboxylate

The title compound was prepared by the method of preparation 17c using the products from preparations 32 and 44.

1H NMR (400MHz, DMSO): δ = 0.95 (t, 3H), 1.05 (t, 3H), 1.40 (s, 9H), 1.78-1.88 (m, 2H), 2.68 (q, 2H), 4.22-4.35 (m, 4H), 4.40 (t, 2H), 5.33 (t, 1H), 7.35 (bs, 1H), 7.52 (bs, 1H), 8.40 (s, 1H), 8.55 (s, 1H), 10.10 (s, 1H)

LRMS (TSP – positive ion) 373.2 (MH^+ - BOC and I)

Anal. Found C, 45.11; H, 5.07; N, 13.56 Calcd for $C_{23}H_{31}O_5N_6I$. 0.2 DCM: C, 45.28; H, 5.14; N, 13.66.

Preparation 53

tert-Butyl 4-(3-(aminocarbonyl)-5-ethyl-4-{[(5-iodo-2-propoxy-3-pyridinyl)carbonyl]amino}-1*H*-pyrazol-1-yl)-1-piperidinecarboxylate

The title compound was prepared using the method of preparation 17b, and the product from preparation 32 in 52% yield (10.3 g).

1H NMR (400MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.10 (t, 3H), 1.45 (s, 9H), 1.85-1.95 (m, 4H), 2.10 (m, 2H), 2.84 (m, 4H), 4.10-4.30 (m, 3H), 4.50 (t, 2H), 5.10 (s, 1H), 6.60 (s, 1H), 8.40 (s, 1H), 8.72 (s, 1H), 10.30 (s, 1H)

LRMS (TSP – positive ion) 628 (MH^+)

$0.2H_2O$: C, 45.04; H, 5.29; N, 15.01%

Preparation 49

N-[5-(Aminocarbonyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-pyrazol-4-yl]-2-ethoxy-5-iodonicotinamide

The title compound was prepared by the method of preparation 13 from the products of preparations 31 and 47 in 88% yield (4.0 g).

1H NMR (300 MHz, $CDCl_3$): δ = 1.2 (t, 3H), 1.5 (t, 3H), 2.4-2.5 (m, 4H), 2.6 (q, 2H), 2.8 (t, 2H), 3.6-3.7 (m, 4H), 4.45 (t, 2H), 4.65 (q, 2H), 5.6 (br s, 1H), 8.3 (br s, 1H), 8.45 (s, 1H), 8.77 (s, 1H), 9.55 (s, 1H).

LRMS (TSP) 544 (MH^+).

Preparation 50

N-[3-(Aminocarbonyl)-1-(4-cyanobenzyl)-5-ethyl-1*H*-pyrazol-4-yl]-2-ethoxy-5-iodonicotinamide

The title compound was prepared from the title compound of preparation 38 and 4-cyanobenylchloride in 83% yield (988 mg).

1H NMR (300 MHz, $CDCl_3$): δ = 1.2 (t, 3H), 1.55 (t, 3H), 2.8 (q, 2H), 3.0 (s, 3H), 3.1 (s, 3H), 4.65 (q, 2H), 4.95 (s, 2H), 5.2 (br s, 1H), 6.6 (br s, 1H), 8.40 (d, 1H), 8.80 (d, 1H), 10.45 (br s, 1H).

LRMS (TSP) 514 (MH^+), 537 (MNa^+).

Preparation 51

N-[3-(Aminocarbonyl)-5-ethyl-1-(2-pyridinylmethyl)-1*H*-pyrazol-4-yl]-5-iodo-2-propoxynicotinamide

The title compound was prepared using the method of preparation 13 and the title compounds of preparations 31 and 4-amino-5-ethyl-1-(2-pyridinylmethyl)-1*H*-pyrazole-3-carboxamide (WO 9849166).

Preparation 47

4-Amino-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-pyrazole-5-carboxamide

The title compound of preparation 46a (16 g, 54 mmol) was dissolved in ethanol (320 ml) and treated with 10% Pd on C (1.5 g) before stirring at RT under 60 psi of hydrogen for 6 h. The catalyst was removed by filtration through Arbocel®, the filtrate concentrated *in vacuo* to an oil which afforded the title compound as a pink solid after trituration with diisopropyl ether (13.18 g, 49.3 mmol).

m.p. 115-7°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.2 (t, 3H), 2.4-2.5 (m, 4H), 2.55 (q, 2H), 2.8 (t, 2H), 3.4 (s, 2H), 3.6-3.65 (m, 4H), 4.45 (t, 2H).

LRMS (TSP) 268 (MH^+).

Analysis: Found C, 53.89; H, 8.04; N, 25.86. Calcd for $C_{12}H_{21}N_5O_2$: C, 53.92; H, 7.92; N, 26.20%

Preparation 48

N-{5-(Aminocarbonyl)-3-ethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-pyrazol-4-yl}-5-iodo-2-propoxynicotinamide

The title compound was prepared by the method of preparation 13 using the title compounds of preparations 31 and 47.

m.p. 180-180.5°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.25 (t, 3H), 1.85-1.95 (m, 2H), 2.4-2.55 (m, 4H), 2.6 (q, 2H), 2.8 (t, 2H), 3.55-3.7 (m, 4H), 4.5 (t, 2H), 4.55 (t, 2H), 5.6 (br s, 1H), 8.25 (br s 1H), 8.5 (s, 1H), 8.75 (s, 1H), 9.5 (s, 1H).

LRMS (TSP) 558 (MH^+).

Analysis: Found C, 45.05; H, 5.23; N, 14.59. Calcd for $C_{21}H_{29}N_6O_4I$.

(m, 2H), 7.3 (br s, 1H), 7.7 (br s, 1H), 8.7 (s, 1H), 9.2 (s, 1H), 9.7 (s, 1H).

LRMS (ES negative ion) 375 $(M-H)^-$.

Analysis: Found C, 50.99; H, 5.36; N, 22.33. Calcd for $C_{16}H_{20}N_6O_5$: C, 51.06; H, 5.36; N, 22.33%

Preparation 46a

3-Ethyl-1-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrazole-5-carboxamide

and

Preparation 46b

5-ethyl-1-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrazole-3-carboxamide

Using the method of preparations 10a and 10b, the title compounds were prepared using 4(2-chloroethyl)morpholine.HCl. The regiochemistry was determined by nOe studies.

3-Ethyl-1-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrazole-5-carboxamide

m.p. 133°C.

1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 2.4-2.45 (m, 4H), 2.75 (t, 2H), 2.9 (q, 2H), 3.55-3.65 (m, 4H), 4.45 (t, 2H), 6.4 (br s, 1H), 7.6 (br s, 1H).

LRMS (TSP) 298 (MH^+).

Analysis: Found C, 48.47; H, 6.47; N, 23.49. Calcd for $C_{12}H_{19}N_5O_4$: C, 48.48; H, 6.44; N, 23.56%

5-ethyl-1-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrazole-3-carboxamide

m.p. 144.9-147.1°C.

1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 2.4-2.5 (m, 4H), 2.8 (t, 2H), 3.0 (q, 2H), 3.55-3.65 (m, 4H), 4.2 (t, 2H), 6.0 (br s, 1H), 7.25 (br s, 1H).

LRMS (TSP) 298 (MH^+).

Analysis: Found C, 48.49; H, 6.47; N, 23.35. Calcd for $C_{12}H_{19}N_5O_4$: C, 48.48; H, 6.44; N, 23.56%

Methyl 5-amino-2-propoxynicotinate

The title compound was prepared from the title compound of Preparation 42 by the method of Preparation 28.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.04 (3H, t), 1.80 (2H, m), 3.40 (2H, s), 3.89 (3H, s), 4.28 (2H, t), 7.57 (1H, s), 7.80 (1H, s).

LRMS (TSP) : 211 $(MH)^+$

Preparation 44

tert-Butyl 3-iodo-1-azetidinecarboxylate

A mixture of *tert*-butyl 3-[(methylsulfonyl)oxy]-1-azetidinecarboxylate (prepared as described in *Synlett* **1998**, 379; 5.0 g, 19.9 mmol), and potassium iodide (16.5 g, 99.4 mmol) in *N,N*-dimethylformamide (25 mL), was heated at 100°C for 42 h. The cooled mixture was partitioned between water and ethyl acetate, and the layers separated. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue azeotroped with xylene. The crude product was purified by flash column chromatography (dichloromethane as eluant) to give the title compound, 3.26 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (s, 9H), 4.28 (m, 2H), 4.46 (m, 1H), 4.62 (m, 2H).

LRMS (TSP) 284 $(MH)^+$

Preparation 45

N-[5-(Aminocarbonyl)-1-methyl-3-propyl-1*H*-pyrazol-4-yl]-2-ethoxy-5-nitronicotinamide

The product of preparation 21 and 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (prepared as described in EP 526 004) were combined using the method of preparation 13.

m.p. 251-3°C.

1H NMR (300 MHz, d_6-DMSO): δ = 0.9 (t, 3H), 1.38 (t, 3H), 1.5-1.7 (m, 2H), 2.5-2.55 (m, partially obscured by DMSO peak), 3.9 (s, 3H), 4.5-4.65

Preparation 40

2-Propoxynicotinic acid

The title compound was prepared in 73% yield from *n*-propanol using the method of Preparation 1.

^{1}H NMR (300 MHz, d_6-DMSO + 1 drop d_1-trifluoroacetic acid) δ = 0.95 (t, 3H), 1.65-1.8 (m, 2H), 4.25 (t, 2H), 7.0 (m, 1H), 8.1 (d, 1H), 8.25 (d, 1H).

Preparation 41

Methyl-2-propoxynicotinate

Diethyl azodicarboxylate (2.2 mL, 14 mmol) was added dropwise to a solution of the title compound of Preparation 40 (2.30 g, 12.7 mmol), triphenylphosphine (3.67 g, 14 mmol) and methanol (0.60 mL, 15 mmol) in tetrahydrofuran (20 mL) and the reaction stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure, the residue triturated with a 20% diethyl ether:pentane solution and then filtered. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (diethyl ether:pentane 50:50 as eluant), to afford the title compound (2.2 g, 11.3 mmol) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.07 (3H, t), 1.86 (2H, m), 3.92 (3H, s), 4.38 (2H, t), 6.93 (1H, m), 8.15 (1H, d), 8.30 (1H, d).

Preparation 42

Methyl 5-nitro-2-propoxynicotinate

The title compound was prepared in 32% yield (after crystallisation from methanol) from the title compound of Preparation 41, using the method of Preparation 20.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.04 (3H, t), 1.84 (2H, m), 3.92 (3H, s), 4.48 (2H, t), 8.88 (1H, s), 9.14 (1H, s).

Preparation 43

Concentration gave a residue which was taken up in ethyl acetate (150 mL) and water (250 mL). The separated aqueous phase was extracted with ethyl acetate (2 x 150 mL), and the combined organics dried over $MgSO_4$, concentrated and purified by column chromatography (dichloromethane:methanol:ammonia (98:2:0.2 to 97:2.5:0.5) as eluant) to afford the title compound as a white solid (2.23 g, 4.5 mol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.3 (t, 3H), 1.55 (t, 3H), 2.3 (s, 6H), 2.8 (t, 2H), 2.9 (q, 2H), 4.2 (t, 2H), 4.6 (q, 2H), 5.25 (br s, 1H), 6.6 (br s, 1H), 8.4 (s, 1H), 8.8 (s, 1H), 10.5 (s, 1H)

LRMS (TSP) 401 (MH^+)

The regioisomers were confirmed by long range ^{1}H-^{13}C correlation experiments (HMBC).

The title compound was prepared from 2-ethoxynicotinic acid using the method of Preparation 3.

^{1}H NMR (400 MHz, d_6-DMSO): δ = 13.2 (br s, 1H), 8.5 (d, 1H), 8.3 (d, 1H), 4.35 (q, 2H), 1.3 (t, 3H)

Preparation 38

N-[5-(Aminocarbonyl)-3-ethyl-1*H*-pyrazol-4-yl]-2-ethoxy-5-iodonicotinamide

The title compound of Preparation 37 (8 g, 27.3 mmol) in dichloromethane (200 mL) was treated with 1-hydroxybenzotriazole hydrate (4.43 g, 32.8 mmol), *N,N*-diisopropylethylamine (14.3 mL, 77.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydro-chloride (6.27 g, 31.7 mmol) and 4-amino-3-ethyl-1*H*-pyrazole-5-carboxamide (prepared as described in WO 98/49166; 3.78 g, 24 mmol), and the resultant mixture stirred at room temperature for 14 h. After washing with water (100 mL), a portion of the title compound was isolated by filtration of the precipitate as a pale brown solid (6.55 g, 15.3 mmol). The organic phase was dried over $MgSO_4$, concentrated and the residue treated with diethyl ether to give further title compound as a pale brown solid (1.65 g, 3.84 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 1.55 (t, 3H), 2.9 (2H, q), 2.65 (2H, q), 5.4 (br s, 1H), 6.75 (br s, 1H), 8.4 (d, 1H), 8.8 (d, 1H), 10.65 (br s, 1H).

LRMS (ES – positive ion) 430 (MH^+).

Preparation 39

N-{3-(Aminocarbonyl)-1-[2-(dimethylamino)ethyl]-5-ethyl-1*H*-pyrazol-4-yl}-2-ethoxy-5-iodonicotinamide

Cesium carbonate (3.3 g, 10.2 mmol) was added to a stirred solution of the title compound of Preparation 38 (4 g, 9.3 mmol) and 2-dimethyl-aminoethylchloride hydrochloride (1.2 g, 11.2 mmol) in *N,N*-dimethyl-formamide (50 mL) and the resultant solution stirred at 80°C for 14 h.

Preparation 36

Benzyl 5-({[5-(aminocarbonyl)-1-methyl-3-propyl-1*H*-pyrazol-4-yl]-amino}carbonyl)-6-propoxy-3-pyridinylcarbamate

A solution of the title compound from Preparation 35 (1.51 g, 4.6 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (1.74 g, 4.6 mmol) and *N,N*-diisopropylethylamine (2.39 mL, 13.7 mmol) in *N,N*-dimethylformamide (20 mL) was added to 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (prepared as described in EP 526 004; 1.0 g, 4.6 mmol) and *N,N*-diisopropylethylamine (2.39 mL, 13.7 mmol) in *N,N*-dimethylformamide (10 mL) and the resultant mixture stirred at room temperature for 24 h. After concentrating *in vacuo*, the mixture was dissolved in ethyl acetate (50 mL), and washed with aq. sodium bicarbonate solution (5%, 50 mL). The nascent solid was removed by filtration and confirmed as product (659 mg, 1.3 mmol). The organic phase was washed with water (50 mL) and brine (25 mL) before drying over $MgSO_4$ and concentrating to a pink solid which was crystallised from hot ethyl acetate to afford further title compound as a white solid (368 mg, 0.7 mmol). The mother liquors were then purified by column chromatography (ethyl acetate:pentane 3:1 as eluant) to afford a further batch of title compound (111 mg, 0.2 mmol).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 0.85 (t, 3H), 0.95 (t, 3H), 1.5-1.6 (m, 2H), 1.7-1.85 (m, 2H), 2.4 (t, 2H), 3.9 (s, 3H), 4.3 (t, 2H), 5.15 (s, 2H), 7.3-7.45 (m, 5H), 7,7 (br s, 1H), 8.2 (br s, 1H), 8.4 (s, 1H), 9.5 (s, 1H), 9.85 (br s, 1H).

LRMS (TSP) 495 (MH^+).

Analysis: found C, 60.19; H, 6.02; N, 16.81. Calcd for $C_{25}H_{30}N_6O_5 \cdot 0.3H_2O$: C, 60.06; H, 6.17; N, 16.81%

Preparation 37

2-Ethoxy-5-iodonicotinic acid

Preparation 34

Methyl 5-{[(benzyloxy)carbonyl]amino}-2-propoxynicotinate

Benzyl chloroformate (6.6 mL, 45.9 mmol) was added dropwise to the title compound of Preparation 43 (9.6 g, 45.9 mmol) and sodium carbonate (4.4 g, 41.4 mmol) in tetrahydrofuran (51 mL) and water (38 mL) with ice-cooling. After 5 h, the reaction mixture was diluted with ethyl acetate (200 mL), the aqueous phase removed, and the remaining organic phase washed with water (200 mL), dried over $MgSO_4$, concentrated, and the brown solid triturated with pentane to give the title compound as a buff solid (13.5 g, 39.3 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.9 (2H, tq), 3.85 (s, 3H), 4.35 (t, 2H), 5.2 (s, 2H), 6.5 (br s, 1H), 7.3-7.4 (m, 5H), 8.25 (2H, br s).

LRMS (TSP) 345 (MH^+).

Preparation 35

5-{[(Benzyloxy)carbonyl]amino}-2-propoxynicotinic acid

A solution of sodium hydroxide (3.12 g, 78 mmol) in water (15 mL) was added to a stirred suspension of the title compound of Preparation 34 (13.55 g, 39 mmol) in methanol (140 mL) and the mixture stirred at room temperature for 18 h. After concentration *in vacuo*, the residue was dissolved in water (100 mL) which was acidified to pH 5 with conc. hydrochloric acid and the precipitate removed by filtration, washed with water and dried. Purification by column chromatography (ethyl acetate:pentane (4:1) as eluant) to gave the title compound as a white solid

(8.9 g, 27 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.0 (t, 3H), 1.8-1.95 (m, 2H), 4.45 (t, 2H), 5.2 (s, 2H), 7.3-7.4 (m, 5H), 7.95 (br s, 1H), 8.4 (d, 1H), 8.5 (br s, 1H), 11.1 (br s, 1H).

LRMS (TSP) 331 (MH^+).

carboxamide (prepared as described in EP 526 004) according the method described in Preparation 13.

m.p. 257-9°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H), 1.15 (t, 3H), 1.6-1.75 (m, 2H), 1.85-1.95 (m, 2H), 2.55 (t, 2H), 405 (s, 3H), 4.5 (t, 2H), 5.45-5.65 (br s, 1H), 7.55-7.65 (br s, 1H), 8.5 (s, 1H), 8.8 (s, 1H), 9.3 (s, 1H).

LRMS (ES – negative ion) 470 (M-H), (ES – positive ion) 472 (MH^+).

Analysis: found C, 43.32; H, 4.62; N, 14.77. Calcd for $C_{17}H_{22}IN_5O_3$: C, 43.32; H, 4.71; N, 14.86%

3 h. The reaction was quenched by the addition of hydrochloric acid (2N), and the mixture then evaporated under reduced pressure. The residue was crystallised from methanol:diethyl ether to afford the title compound, (800 mg, 45%) as an off-white solid.

^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.20 (s, 6H), 7.18 (d, 1H), 8.18 (m, 2H).

Preparation 31

2-Propoxy-5-iodonicotinic acid

The title compound was prepared from the title compound of Preparation 40 using the method of Preparation 3.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 3H), 1.85-2.0 (m, 2H), 4.5 (t, 2H), 8.5 (s, 1H), 8.6 (s, 1H).

Analysis: found C, 35.16; H, 3.19; N, 4.46. Calcd for $C_9H_{10}INO_3$: C, 35.19; H, 3.28; N, 4.56%

Preparation 32

N-[3-(Aminocarbonyl)-5-ethyl-1*H*-pyrazol-4-yl]-5-iodo-2-propoxy-nicotinamide

The title compound was prepared from 2-propoxy-5-iodonicotinic acid (see Preparation 31 above) and 4-amino-3-ethyl-1*H*-pyrazole-5-carboxamide (prepared as described in WO 98/49166) according to the method described in Preparation 13.

^{1}H NMR (300 MHz, d_4-MeOH): δ = 1.0 (t, 3H), 1.25 (t, 3H), 1.85-2.0 (m, 2H), 2.8 (q, 2H), 4.5 (t, 2H), 8.5 (s, 1H), 8.6 (s, 1H).

LRMS (TSP) 444 (MH^+).

Preparation 33

N-[5-(Aminocarbonyl)-1-methyl-3-propyl-1*H*-pyrazol-4-yl]-5-iodo-2-propoxynicotinamide

The title compound was prepared from 2-propoxy-5-iodonicotinic acid (see Preparation 31 above) and 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-

0.24 mol) in *N,N*-dimethylformamide (200 mL) was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure and the residue azeotroped with xylene. The resulting brown gum was triturated with hot ethyl acetate (6 x 400 mL) and hot methanol/dichloromethane (4 x 500 mL), the resulting suspensions filtered and the combined filtrates evaporated under reduced pressure. The residual brown solid was purified by column chromatography on silica gel, using an elution gradient of ethyl acetate:hexane (30:70 to 100:0) to afford the title compound, (11.5 g, 31%) as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03 (s, 3H), 5.88 (s, 1H), 7.80 (s, 1H), 8.25 (s, 1H).

Preparation 29

4-Amino-2-methyl-pyrazole-5-carboxamide

A mixture of the title compound of Preparation 28 (5.0 g, 30.0 mmol) and 10% palladium on charcoal (500 mg) in methanol (200 mL) was hydrogenated at 206.8 kPa (30 psi) and 50°C for 18 h. The cooled mixture was filtered through Arbocel® , the filter pad washed with methanol, and the combined filtrate evaporated under reduced pressure to afford the title compound, (4.2 g, 100%) as a pink solid.

^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.72 (s, 3H), 4.60 (s, 2H), 6.88 (s, 1H), 7.05 (m, 2H).

Preparation 30

6-(Dimethylamino)pyridin-3-yl boronic acid dihydrochloride

n-Butyllithium (5.3 mL, 1.6M in hexanes, 8.5 mmol) was added dropwise to a cooled (-70°C) solution of 5-bromo-2-(dimethylamino)pyridine (J. Org. Chem. 1983; 48; 1064) (1.5 g, 7.46 mmol) in tetrahydrofuran (20 mL), and the solution stirred for 30 minutes. A solution of triisopropyl borate (2.57 mL, 11.2 mmol) in tetrahydrofuran (4 mL) was added dropwise, and the reaction then allowed to warm to room temperature over

1 = reaction heated under reflux for 18 hours.

Example 78

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-2-methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Acetic hydrazide (80mg, 1.08mmol), followed by triethylamine (0.34ml, 2.44mmol) were added to a suspension of the title compound of preparation 158 (500mg, 0.98mmol) in dichloromethane (15ml), and the reaction stirred at room temperature for 4 hours. The reaction mixture was partitioned between dichloromethane and aqueous sodium bicarbonate solution, and the layers separated. The aqueous phase was extracted with dichloromethane, and the combined organic solutions dried (Na_2SO_4) and evaporated under reduced pressure, to give a solid, 520mg. Thionyl chloride (5ml) was added to this intermediate hydrazide (350mg), and the solution stirred at 80°C for 3 hours. The cooled reaction was partitioned between dichloromethane and aqueous sodium bicarbonate solution, and the layers separated. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (99:1 to 94:6) to give the title compound, 55mg.

δ ($CDCl_3$) : 1.01 (3H, t), 1.60 (3H, t), 2.41 (2H, q), 2.58 (4H, m), 2.75 (3H, s), 3.17 (4H, m), 4.58 (3H, s), 4.80 (2H, q), 8.69 (1H, s), 9.19 (1H, s), 10.88 (1H, s).

Example 79

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-pyridin-3-yl]-2-methyl-3-(tetrahydrofuran-2-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound from example 61 (80mg, 0.16mmol) and 10% palladium on charcoal (10mg) in ethanol (4.5ml) and water (0.5ml) was hydrogenated at 60 psi (414 kPa) and 40°C for 18 hours. The reaction mixture was filtered through Celite®, and the filtrate evaporated under reduced pressure to afford the title compound, (27mg, 32%).

δ ($CDCl_3$) : 1.01 (3H, t), 1.59 (3H, t), 2.15 (1H, m), 2.26 (1H, m), 2.40 (3H, m), 2.56 (4H, m), 2.86 (1H, m), 3.14 (4H, m), 3.98 (1H, m), 4.02 (1H, m), 4.20 (3H, s), 4.77 (2H, q), 5.36 (1H, m), 8.62 (1H, d), 9.00 (1H, d), 10.68 (1H, s).

LRMS : m/z 518 $(M+1)^+$

Example 80

3-Ethoxy-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Sodium nitrite (12mg, 0.18mmol) was added to a cooled (-10°C) solution of the title compound of preparation 120 (40mg, 0.12mmol) in acetic acid (0.45ml) and concentrated hydrochloric acid (0.45ml) and the solution allowed to warm to 0°C over 2 hours. The solution was re-cooled to -20°C, liquid sulphur dioxide (0.36ml) and a solution of copper (II) chloride (48mg, 0.48mmol) in water (2ml) and acetic acid (1ml) added, and the reaction then allowed to warm to room temperature over 2 hours. The mixture was extracted with dichloromethane, the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and azeotroped with toluene. The brown residue was dissolved in ethanol (10ml), N-ethylpiperazine (50µl, 0.38mmol) added and the reaction stirred

at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the crude product purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:0.5) to give the title compound, (12mg, 20%).

δ ($CDCl_3$) : 1.02 (3H, t), 1.57 (6H, m), 2.41 (2H, q), 2.57 (4H, m), 3.12 (4H, m), 3.90 (3H, s), 4.74 (2H, q), 4.88 (2H, q), 8.60 (1H, d), 8.92 (1H, d), 10.56 (1H, s).

LRMS : m/z 492 $(M+1)^+$

Example 81

5-[2-n-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethoxy-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Potassium bis(trimethylsilyl)amide (10mg, 0.05mmol) was added to a suspension of the title compound of example 80 (10mg, 0.02mmol) in n-butanol (4ml), and the reaction mixture heated under reflux for 6 hours. The cooled mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (98:2:0.5) as eluant, to afford the title compound, (8mg, 76%).

δ ($CDCl_3$) : 1.02 (6H, t), 1.57 (5H, m), 1.96 (2H, m), 2.42 (2H, q), 2.56 (4H, m), 3.13 (4H, m), 3.90 (3H, s), 4.65 (2H, t), 4.88 (2H, q), 8.60 (1H, s), 8.90 (1H, s), 10.53 (1H, s).

LRMS : m/z 520 $(M+1)^+$

Example 82

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)-pyridin-3-yl]-3-(1-ethoxyvinyl)-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A mixture of the title compound or preparation 101 (100mg, 0.19mmol), lithium chloride (80mg, 1.9mmol), copper (I) iodide (6mg, 0.03mmol) and (1-ethoxyvinyl)(tri-n-butyl)stannane (90mg, 0.247mmol) in dioxan (10ml) was de-gassed and placed under an atmosphere of nitrogen. Tetrakis(triphenylphosphine)palladium (0) (20mg, 0.017mmol) was added, and the reaction heated under reflux for 5 hours. The cooled mixture was concentrated under reduced pressure, and the residue stirred vigorously in a solution of ethyl acetate:10% aqueous potassium fluoride solution for 10 minutes. The resulting suspension was filtered through Arbocel®, and the filtrate separated. The organic layer was washed with 10% aqueous potassium fluoride solution, then brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by medium pressure column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 98:2) to afford the title compound (84mg, 85%) as a foam.

δ ($CDCl_3$) : 1.02 (3H, t), 1.46 (3H, t), 1.58 (3H, t), 2.41 (2H, q), 2.57 (4H, m), 3.15 (4H, m), 4.02 (2H, q), 4.24 (3H, s), 4.69 (1H, d), 4.77 (2H, q), 5.23 (1H, d), 8.62 (1H, d), 9.06 (1H, d), 10.70 (1H, s).

LRMS : m/z 518 $(M+1)^+$

Example 83

N,2-Dimethyl-5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidine-3-carboxamide

A mixture of the title compound of preparation 159 (50mg, 0.108mmol), acetyl chloride (7µl, 0.108mmol) and pyridine (9µl, 0.11mmol) in

dichloromethane (2ml) was stirred at room temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 80:20) to afford the title compound (45mg, 82%).

δ ($CDCl_3$) : 1.08 (3H, m), 1.58 (3H, t), 2.38 (3H, s), 2.44-2.70 (6H, m), 3.18 (4H, m), 4.01 (3H, s), 4.74 (2H, q), 8.60 (1H, d), 8.95 (1H, d), 10.67 (1H, s).

LRMS : m/z 504 $(M+2)^+$

Biological Activity

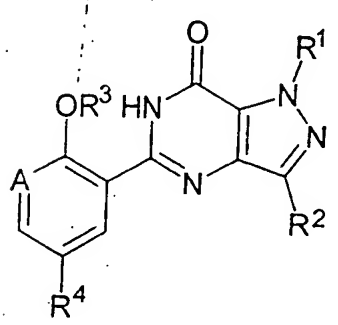
Compounds of the invention were found to have *in vitro* activities as inhibitors of cGMP PDE5 with IC_{50} values of less than about 100 nM.

The following Table illustrates the *in vitro* activities for a range of compounds of the invention as inhibitors of cGMP PDE5.

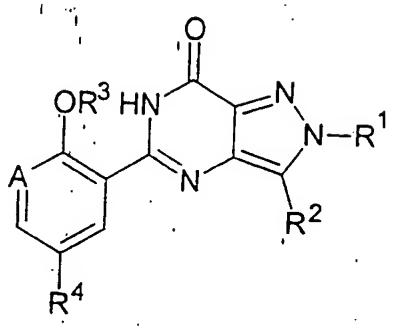
Example	IC_{50} (nM)
5	2.80
8	4.10
19	3.40
33	2.80
42	2.26

Claims

1. A compound of formula IA, or of formula IB:



IA



IB

wherein

A represents CH or N;

R^1 represents H, lower alkyl, Het, alkylHet, aryl or alkylaryl, which latter five groups are all optionally substituted (and/or, in the case of lower alkyl, optionally terminated) by one or more substituents selected from halo, cyano, nitro, lower alkyl, OR^5, $C(O)R^6$, $C(O)OR^7$, $C(O)NR^8R^9$, $NR^{10a}R^{10b}$ and $SO_2NR^{11a}R^{11b}$;

R^2 represents $C(O)NR^{12}R^{13}$, $C(O)OR^{12}$, $NR^{12}R^{13}$, $N(H)SO_2R^{12}$, $N(H)SO_2NR^{12}R^{13}$, $N(H)C(O)R^{12}$, OR^{12a}, lower alkyl (which alkyl group is interrupted by one or more of O, S or $N(R^{12})$ and/or substituted or terminated by $C(O)NR^{12}R^{13}$, $C(O)OR^{12}$ or aryl or Het^1), cyano, aryl or Het^1;

R^3, R^{12} and R^{13} independently represent H or lower alkyl, which alkyl group is optionally substituted and/or optionally terminated by one or more substituents selected from aryl, Het, halo, cyano, nitro, OR^5, $C(O)R^6$, $C(O)OR^7$, $C(O)NR^8R^9$, $NR^{10a}R^{10b}$ and $SO_2NR^{11a}R^{11b}$;

R^4 represents $SO_2NR^{14}R^{15}$;

R^{14} and R^{15}, together with the nitrogen to which they are attached, form Het;

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains at least one nitrogen atom and, optionally, one or more further heteroatoms selected from nitrogen, oxygen and sulphur;

Het^1 represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains at least one nitrogen atom or at least one oxygen atom and, optionally, one or more further heteroatoms selected from nitrogen, oxygen and sulphur; and

R^5, R^6, R^7, R^8, R^9, R^{11a}, R^{11b} and R^{12a} independently represent, at each occurrence when used herein, H or lower alkyl;

R^{10a} and R^{10b}, at each occurrence when used herein, either independently represent, H or lower alkyl or, together with the nitrogen atom to which they are attached, represent azetidinyl, pyrollidinyl or piperidinyl;

or a pharmaceutically, or a veterinarily, acceptable derivative thereof.

2. A compound as claimed in Claim 1, wherein R^1 represents H, a linear, branched, cyclic, acyclic and/or part cyclic/acyclic lower alkyl group, alkylHet, or alkylaryl.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^2 represents a linear or branched, optionally unsaturated lower alkyl group (which alkyl group is optionally interrupted by one or more of O, S or $N(R^{12})$), $C(O)NR^{12}R^{13}$, $NR^{12}R^{13}$, $N(H)C(O)R^{12}$, OR^{12a}, aryl or Het^1.

4. A compound as claimed in any one of the preceding claims, wherein R^3 represents linear, branched, cyclic and/or acyclic lower alkyl

which is optionally substituted or terminated by one or more substituents selected from Het or OR^5.

5. A compound as claimed in any one of the preceding claims, wherein R^{12} and R^{13} independently represent H, or linear or branched lower alkyl, provided that, in the case where R^2 represents $NR^{12}R^{13}$, R^{12} and R^{13} do not both represent H.

6. A compound as claimed in any one of the preceding claims, wherein R^{14} and R^{15}, together with the nitrogen to which they are attached represent 4-R^{16}-piperazinyl, in which R^{16} represents H or lower alkyl, which latter group is optionally substituted or terminated by one or more substituents selected from aryl, Het, halo, cyano, nitro, OR^5, $C(O)R^6$, $C(O)OR^7$, $C(O)NR^8R^9$, $NR^{10a}R^{10b}$, $SO_2NR^{11a}R^{11b}$ and $N(H)SO_2R^{12}$ wherein R^5, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, R^{11b} and R^{12} are as defined in Claim 1.

7. A compound as defined in any one of Claims 1 to 6 for use as a pharmaceutical.

8. A compound as defined in any one of Claims 1 to 6 for use as an animal medicament.

9. A formulation comprising a compound as defined in any one of Claims 1 to 6 in admixture with a pharmaceutically or veterinarily acceptable adjuvant, diluent or carrier.

10. A formulation as claimed in Claim 9, which is a pharmaceutical formulation.

11. A formulation as claimed in Claim 9, which is a veterinary formulation.

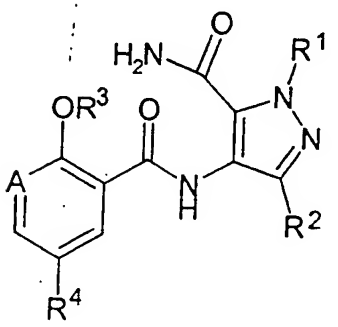
12. The use of a compound as defined any one of Claims 1 to 6 for the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which inhibition of cGMP PDE5 is desired.

13. A method of treating or preventing a medical condition for which inhibition of cGMP PDE5 is desired, which comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 6 to a patient in need of such treatment.

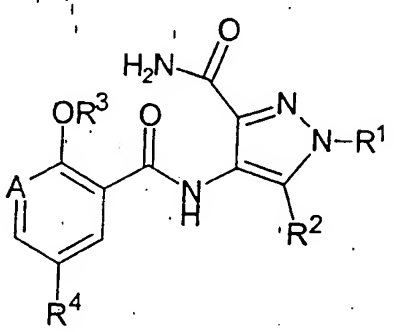
14. Use as claimed in Claim 12, or method as claimed in Claim 13, wherein the condition is male erectile dysfunction, female sexual dysfunction, premature labour, dsymenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable or unstable variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, a disease characterised by disorders of gut motility, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction.

15. A process for the preparation of a compound of formula IA, or of formula IB, as defined in Claim 1, which comprises:

(a) cyclisation of a corresponding compound of formula IIA, or of formula IIB, respectively:



IIA



IIB

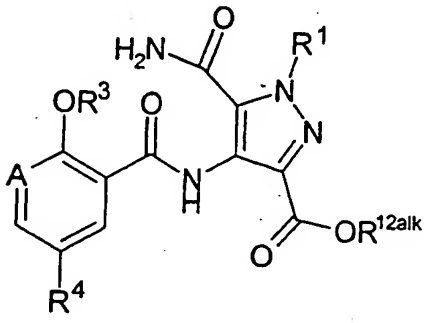
wherein R^1, R^2, R^3, R^4 and A are as defined in Claim 1;

(b) for compounds of formulae IA and IB, in which R^2 represents $C(O)NR^{12}R^{13}$, reaction of a corresponding compound of formula IA, or of formula IB, in which R^2 represents C(O)OH (or a carboxylic acid derivative thereof) with a compound of formula

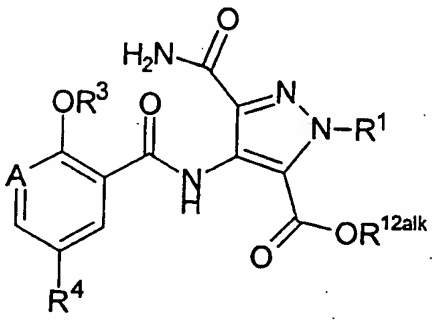
$HNR^{12}R^{13}$,

in which R^{12} and R^{13} are as defined in Claim 1;

(c) for compounds of formulae IA and IB, in which R^2 represents $C(O)OR^{12}$, cyclisation of a corresponding compound of formula VIA, or of formula VIB, respectively:



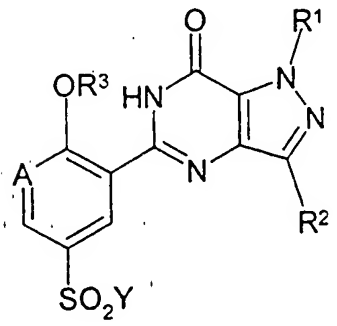
VIA



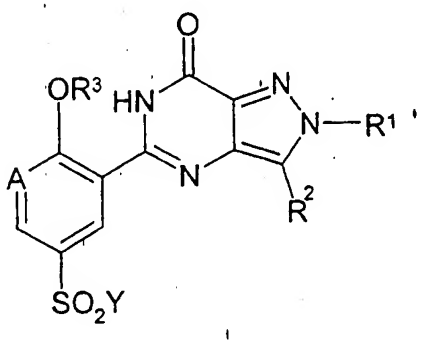
VIB

wherein R^1, R^3, R^4 and A are as defined in Claim 1, and R^{12alk} represents an optionally substituted lower alkyl group, followed by removal of the alkyl group R^{12alk} (if required) by hydrolysis, and/or (if required) exchange with a further optionally substituted alkyl group;

(d) reaction of a corresponding compound of formulae VIIIA, or of formula VIIIB, respectively:



VIIIA



VIIIB

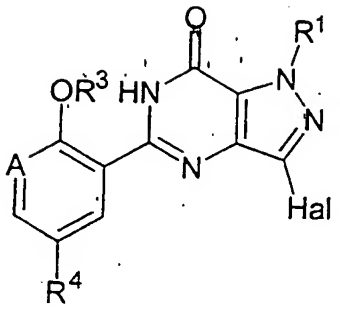
wherein Y is a leaving group, and R^1, R^2, R^3 and A are as defined in Claim 1, with a compound of formula IX:

$R^{14}R^{15}NH$ IX

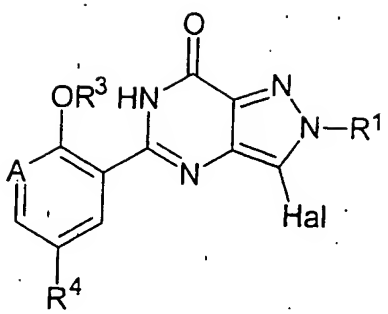
wherein R^{14} and R^{15} are as defined in Claim 1;

(e) for compounds of formulae IA and IB, in which R^1 represents lower alkyl, alkylHet or alkylaryl, alkylation of a corresponding compound of formula IA, or of formula IB, respectively, in which R^1 represents H;

(f) for compounds of formulae IA and IB, in which R^2 represents lower alkyl (which alkyl group is branched and unsaturated at the carbon atom that is attached to the rest of the molecule), $NR^{12}R^{13}$, cyano, aryl or Het^1 (which Het^1 group is either aromatic or unsaturated at the carbon atom that is attached to the rest of the molecule), cross-coupling of a corresponding compound of formula XXIIIA, or of formula XXIIIB, respectively:



XXIIIA



XXIIIB

wherein Hal represents Cl, Br or I and R^1, R^3, R^4 and A are as defined in Claim 1, using a compound of formula

$R^{2a}M$

wherein R^{2a} represents lower alkyl (which alkyl group is branched and unsaturated at the carbon atom that is attached to M), $NR^{12}R^{13}$, cyano, aryl or Het^1 (which Het^1 group is either aromatic or unsaturated at the carbon atom that is attached to M), R^{12} and R^{13} are as defined in Claim 1 and M represents an optionally substituted metal or boron group, which group is suitable for cross-coupling reactions;

(g) for compounds of formulae IA and IB in which R^2 represents $N(H)C(O)R^{12}$, acylation of a corresponding compound of formula IA or IB in which R^2 represents NH_2, using a compound of formula XXVI,

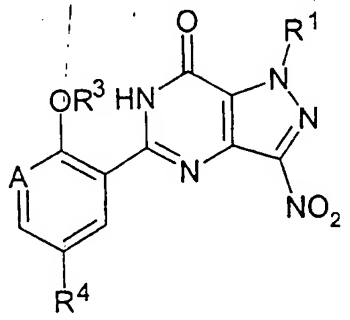
$L^1C(O)R^{12}$ XXVI

in which L^1 represents a leaving group and R^{12} is as defined in Claim 1;

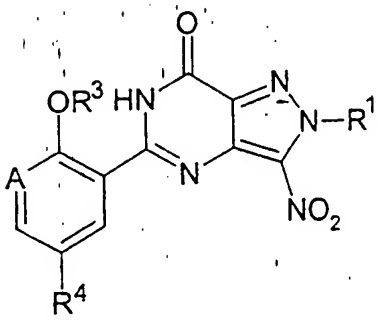
(h) for compounds of formulae IA and IB in which R^2 represents $NR^{12}R^{13}$ in which one of R^{12} and R^{13} does not represent H, alkylation of a corresponding compound of formula IA or IB in which R^2 represents NH_2;

(i) for compounds of formulae IA and IB in which R^2 represents $NR^{12}R^{13}$ in which one of R^{12} and R^{13} does not represent H, reductive amination of a compound of formula IA or IB in which R^2 represents NH_2, using an appropriate carbonyl compound;

(j) for compounds of formulae IA and IB in which R^2 represents NH_2, reduction of a corresponding compound of formula XXVIIA, or of formula XXVIIB, respectively:



XXVIIA



XXVIIB

wherein A, R^1, R^3 and R^4 are as defined in Claim 1;

(k) conversion, removal or introduction of a substituent on an aryl, or a Het or Het^1, group in, or on the phenyl/pyridinyl, or pyrazolo, unit of, a compound of formula IA or IB;

(l) conversion of one R^3 group to another by alkoxide exchange;

(m) for compounds of formula IA or IB in which R^{14} and R^{15}, together with the nitrogen to which they are attached, form a 4-R^{16}-piperazinyl group in which R^{16} represents alkyl, alkylation of a corresponding compound of formula IA or IB in which R^{16} represents hydrogen; or

(n) deprotection of a protected derivative of a compound of formula IA or of formula IB.

16. A compound of formula IIA, or formula IIB, as defined in Claim 15.

17. A compound of formula VIA, or formula VIB, is as defined in Claim 15.

18. A compound of formula VIIIA, or formula VIIIB, as defined in Claim 15.

19. A compound of formula XXIIIA, or formula XXIIIB, as defined in Claim 15.

20. A compound of formula XXVIIA, or formula XXVIIB, as defined in Claim 15.

INTERNATIONAL SEARCH REPORT

	International Application No PCT/IB 99/01706

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 C07D231/14 C07D401/12
//(C07D487/04,239:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 463 756 A (PFIZER LTD) 2 January 1992 (1992-01-02) page 3, line 5 - line 14; claims 1,4,7; example 48	1,9,12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2000	02/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/01706

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12 to 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee. this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/01706

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